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Open Label, Phase II Pilot Study of Immune Checkpoint Inhibition with Pembrolizumab in Combination with PARP Inhibition with Olaparib in Advanced BRCA-mutated or HDR-defect Breast Cancers

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Protocol Version #9 dated 05DEC2023

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations and ICH guidelines.

Principal Investigator (PI) Name: _____

Signature: _____ **Date:** _____

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LIST OF ABBREVIATIONS

AE	Adverse Event
ALT	Alanine Aminotransferase
ALC	Absolute Lymphocyte Count
AST	Aspartate Aminotransferase
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CR	Complete Response
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose Limiting Toxicity
DSMC	Data and Safety Monitoring Committee
ECOG	Eastern Cooperative Oncology Group
FDA	Food and Drug Administration
HDR	Homology-directed repair
H&P	History & Physical Exam
HRPP	Human Research Protections Program
IV (or iv)	Intravenously
NCI	National Cancer Institute
ORR	Overall Response Rate
OS	Overall Survival
PD	Progressive Disease
PFS	Progression Free Survival
PR	Partial Response
SAE	Serious Adverse Event
SD	Stable Disease

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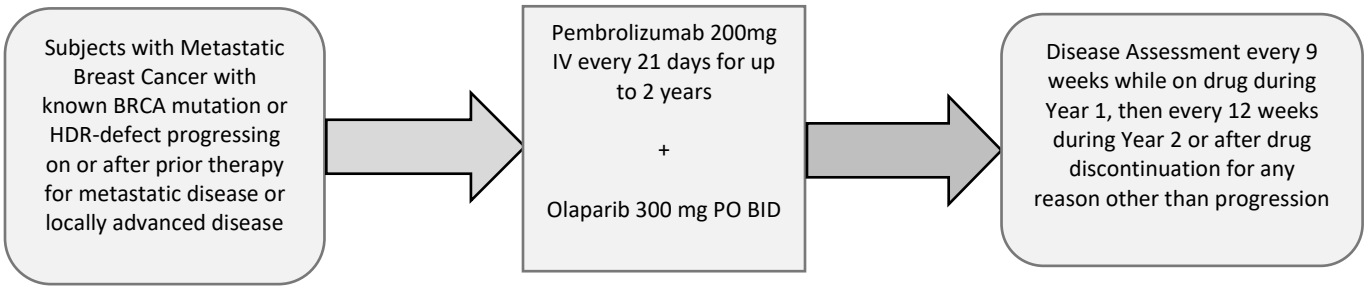
STUDY SCHEMA



STUDY SUMMARY

Abbreviated Title	Pembrolizumab plus olaparib in advanced BRCA-mutated or HDR-defect breast cancer
Trial Phase	II
Clinical Indication	Therapy for metastatic disease after progression on at least one line of prior therapy
Trial Type	Pilot Study - Open label phase II
Type of control	N/A
Route of administration	Intravenous infusion (pembrolizumab), oral (olaparib)
Trial Blinding	N/A
Treatment Groups	Advanced breast cancer with BRCA germline or somatic mutation or HDR-defect
Number of trial subjects	20 (pilot study)
Estimated Enrollment Period	36 months
Estimated duration of trial	42 months
Duration of Participation	2-24 months
Main Eligibility Criterion	Female and Male patients with advanced BRCA-mutated or HDR-defect breast cancer progressing on or after prior therapy for metastatic disease or locally advanced disease; Prior therapy is defined as follows: for triple negative breast cancer – progressing after at least 1 line of any prior chemotherapy; for HER2 positive disease must have progressed after at least two HER2 directed therapies in the metastatic setting including ado-trastuzumab emtansine (T-DM1); for hormone receptor positive disease (ER, PR, or both) must have progressed after a CDK4/CDK6 inhibitor plus hormonal therapy. Patients with progression within 12 months from previous neoadjuvant or adjuvant treatment could be enrolled in the study as 1st line therapy in metastatic setting.

1.0 BACKGROUND AND RATIONALE

1.1 Disease Background

Breast cancer due to germline BRCA 1 or BRCA2 mutation represents approximately 5-10% of the breast cancer population. BRCA 1 and 2 germline mutations are readily determined through commercially available testing of blood and buccal cell DNA. While all breast cancer molecular subtypes may occur in BRCA mutation carriers, it is recognized that approximately 70% of breast cancers developing in BRCA 1 carriers are likely to be triple negative, while over 50% of breast cancer developing in BRCA 2 carriers are estrogen receptor positive. HER2 positive breast cancers may also occur with either BRCA 1 or BRCA2 mutations at a frequency of 10-13% [1]. Historically, breast cancer in BRCA mutation carriers has not been treated differently than breast cancer occurring “sporadically”, according to standard of care guidelines [2, 3]. An inhibitor of the poly (ADP) ribose polymerase (PARP) 1 enzyme, olaparib[4], has been FDA-approved for use in BRCA-mutated ovarian cancer, and clinical trials were recently conducted with these compounds in breast cancer [5]. In 2018, the FDA approved olaparib for germline BRCA-mutated metastatic breast cancer [21]. Response rates with PARP inhibitors in BRCA-mutated breast cancer have ranged from 0 to 41%, with a median progression free survival of 6 months [6, 7]. There remains a significant unmet need for therapy with specific benefit in BRCA-mutated breast cancer. Immunotherapy may offer a targeted therapy with less toxicity than chemotherapy, and potentially greater efficacy for this population with an unmet need for targeted therapy approaches. Positive results in this cohort would be of major clinical research interest and benefit to this population.

The histopathology of BRCA-associated breast cancer suggests a role for the immune system in BRCA biology, based on several observations. Lymphocytic infiltrates are pathognomonic of medullary carcinoma of the breast, a subtype highly associated with BRCA 1 mutation, and lymphocytic infiltrates are commonly noted in BRCA-mutated cancers [8]. More recently the role of the immune system, tumor infiltrating lymphocytes (TILs), and the PD-1/PDL-1 pathway has been studied in breast cancer in general [9]. Of 116 breast cancers, 45% expressed PDL-1, with variation by molecular profile: 59% of triple negative, 33% of estrogen positive and 20% of HER2 positive breast cancers expressed PDL-1. TILs expressing PD-1 were also observed, with the highest proportion having concurrent expression of PD-1 TILs and PDL-1 tumor cells (45%) seen in triple negative breast cancer (TNBC). The only reported analysis of PDL-1 expression in BRCA mutated breast cancer to date indicated in a small subset of triple negative breast cancers, a significant correlation of PD-L1 and BRCA germline mutation, with 7 of 7 BRCA1 mutated breast cancers overexpressing PD-L1[10].

Additional data regarding the expression of PDL-1 in BRCA-mutated cancers have been obtained through a study in collaboration with Merck and Cedars-Sinai Medical Center, for which Dr. Audeh was the PI [11]. A cohort of 30 primary breast cancer tumor samples obtained prior to treatment from germline BRCA mutation carriers (identified previously by genetic testing) were identified within the Cedars-Sinai Pathology Department and were analyzed for relevant immune biomarkers through collaboration with Merck. The laboratory project, funded by Merck, assessed the expression of immune biomarkers PDL-1 and PD-1 using Merck-developed antibodies. The results of the study were as follows: Twenty (20) tumors were from BRCA 1 mutations carriers, and 10 were BRCA2. Sixteen (16) were basal type breast cancer (13 BRCA1, 3 BRCA2), 14 were estrogen receptor positive(ER+)(7 BRCA1, 7BRCA2), with 7 Luminal A and 7 Luminal B. There were no HER2 amplified tumors in the cohort. PD1 expression was observed in 11/30 (37%) of the cohort, and PDL1 expression was detected in 21/30 (70%) of the cohort. PDL1 expression was seen in 15/20 (75%) of tumors from BRCA1 mutation carriers, and 6/10 (60%) of tumors from BRCA2 carriers. PDL1 expression was present in 13/16 (81%) basal tumors and 8/14 (57%) ER+ tumors. Within the cohort of PDL1 expressing cancers, 7/21 (33%) were scored as “high” or “very high”, 5 basal breast cancers and 2 ER+ cancers. The study therefore identified a high rate of PDL1 expression in untreated primary breast cancers with germline BRCA1 and BRCA2 mutations, regardless of intrinsic subtype. PDL-1 expression, in association with other relevant biomarkers, in BRCA-mutated cancers may predict a dependence

on immune suppression for tumor survival, and may predict responsiveness to immune checkpoint inhibition with pembrolizumab.

Evaluation of targeted therapy specific to the biology of BRCA-mutated cancers has been limited to the use of PARP inhibition, which acts through the mechanism of “synthetic lethality”, inducing additional DNA damage and cytotoxicity in cells with homologous repair defects (HRD), and which produces a variety of dose-limiting toxicities, primarily hematologic.

Immunotherapy may offer a targeted therapy with less toxicity, and potentially greater efficacy for this population with an unmet need for targeted therapy approaches. Positive results in this cohort would be of major clinical research interest and benefit to this population.

Combining PARP inhibitors and immunotherapy is a current treatment tested in several studies and tumor types. Rationale derives from the observation that PARP inhibitors enhanced cancer’s ability to produce PD-L1 which enhances the efficacy of immunotherapy (Pd-1 and PDL1 inhibitors). In clinical studies tolerability of the combination is very good with no overlapping toxicities [25-28]. Due to evidence of combinatorial efficacy with the combination, patients previously exposed to PARP inhibitors will remain eligible as the patients PARP inhibitors naïve.

Patients with ER+ disease benefit from continuous hormonal inhibition. Studies show that combination therapy with PARP inhibition and anti-estrogens is safe and there are no interactions [29-30]. Therefore, this study will allow continuation of anti-estrogen therapy for patients with ER+ disease. While there is pre-clinical data on the combination of PARP inhibition and trastuzumab antitumor activity in HER2+ disease [31], due to a lack of safety data, subjects with HER2+ disease will be required to discontinue trastuzumab therapy.

1.2 Study Agent(s) Background and Associated Known Toxicities

1.2.1 Pembrolizumab

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades [32]. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells / FoxP3+ regulatory T-cells (T-regs) correlates with improved prognosis and long-term survival in many 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 [33-34].

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an Ig superfamily member related to CD28 and CTLA-4 which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD L2) [35-36].

The structure of murine PD-1 has been resolved [37]. PD-1 and family members are type I transmembrane glycoproteins containing an Ig Variable-type (V-type) domain responsible for ligand binding and a cytoplasmic tail which is 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 (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM). Following T-cell stimulation, PD 1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3ζ, PKCθ and ZAP70 which are involved in the CD3 T-cell signaling cascade [36; 38-40]. The mechanism by which PD-1 down modulates T-cell responses is similar to, but distinct from that of CTLA-4 as both molecules regulate an overlapping set of signaling proteins [41-42]. As a

consequence, the PD 1/PD-L1 pathway is an attractive target for therapeutic intervention in breast cancer.

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

Refer to the Investigator's Brochure for Preclinical and Clinical data.

1.2.2 Olaparib

Investigators should be familiar with the current olaparib package insert.

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 tumours with deficiencies in DNA repair mechanisms. PARP enzymes are essential for repairing DNA single strand breaks (SSBs). Inhibiting PARPs leads to the persistence of SSBs, which are then converted to the more serious DNA double strand breaks (DSBs) during the process of DNA replication. During the process of cell division, DSBs can be efficiently repaired in normal cells by homologous recombination repair (HR). Tumours 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 tumour types, olaparib may offer a potentially efficacious and less toxic cancer treatment compared with currently available chemotherapy regimens.

BRCA1 and BRCA2 defective tumours are intrinsically sensitive to PARP inhibitors, both in tumour models in vivo [43-44] and in the clinic [45]. The mechanism of action for olaparib results from the trapping of inactive PARP onto the single-strand breaks preventing their repair [46-47]. 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 tumour 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.

Tumors with HDR-defect (homology-related repair) have the same propensity to be sensitive to PARP inhibitors as the BRCA mutated tumors. This has been demonstrated in several studies and mechanistically explained [22-24]. Two clinical studies, reported recently have confirmed antitumor activity with PARP inhibitors in tumors with HRD defect (but not necessary BRCA mutated). First study (TBCRC 048) published in JCO 2020 by N Tung presented responses to different somatic and germline mutations with PARP inhibitors treatment. Similar responses were seen in the somatic vs germline cohort in BRCA and other HRD defects tumors. A second study SWOG 1416 presented at ASCO 2020 revealed that addition of a PARP inhibitor, in this case Veliparib to chemotherapy in BRCA like triple negative metastatic breast cancer patients has similar efficacy compared to BRCA population.

1.3 Tempus HRD

The Tempus HRD detection approach is a model used in conjunction with data from the Tempus|xT Solid Tumor + Normal test, a 648- gene NGS panel spanning 3.6 Mb of DNA. Therefore, if a physician orders xT to identify actionable mutations in their patient's tumor, no additional tissue is required to process an HRD status. The laboratory developed test is performed using Tempus DNA sequencing data to determine deleterious BRCA1/2 mutations, BRCA1/2-specific LOH, and somatic GW LOH, culminating in an HRD score that indicates each patient's likelihood for PARPi response. Additionally, the Tempus HRD report includes results from a variant assessment of 16 other HR-related genes (18 total) conducted as part of the xT testing.

1.4 Rationale

The proposed trial will evaluate the use of immunotherapy in a population with incurable advanced breast cancer associated with a germline or somatic BRCA mutation or HDR-defect, in combination with targeted therapy with olaparib. The genomic instability of BRCA-mutated breast cancer suggests probable increased neoantigen production and antigenicity, and predicts a dependence on immune suppression for carcinogenesis and tumor growth.

Blockade of the inhibitory immune checkpoint controlled by programmed cell death protein 1 (PD-1) and its ligand (PDL-1) has produced clinical responses in a number of malignancies, most significantly melanoma, non-small cell carcinoma, renal cell carcinoma[12] [13]and ovarian cancer [14]. In breast cancer, preliminary data from a phase Ib trial of 32 women with TNBC treated with pembrolizumab at 10mg/kg every 2 weeks yielded a response rate of 18.5%[15]. Biomarkers for response to PD-1 directed therapy may be PDL-1 overexpression[16] [17],as well as possibly other histologic and genomic features. Genomically, the tumors in which responses were seen (melanoma, NSCLC, RCC and TNBC) are also known to have a high degree of genomic instability and mutational load relative to other malignancies [18]. A high mutation rate is likely to produce neoantigens, to which an immune response would be generated, and would be expected to produce evolutionary selection pressure favoring tumors which are able to block the resulting immune response. Therefore, it is hypothesized that genomically unstable tumors may be more likely to utilize inhibition of the immune response through upregulation of PDL-1.

Tumors characterized by intrinsic genomic instability and high mutational load include those with mismatch repair (MMR) defects and those with homologous recombination defects due to BRCA 1 or 2 gene germline mutations. The present study proposes a proof of concept trial in BRCA-mutated breast cancers.

Similar to the previously observed pembrolizumab-responsive tumors, BRCA-mutated cancers are known to be highly genomically unstable[19] [20] and are also characterized histologically by robust lymphocytic infiltrates. It is hypothesized that the genomic instability and high mutation rate in BRCA-mutated cancers results in neoantigens, eliciting a host immune response and selecting for mechanisms for immune escape, such as PDL-1 overexpression.

Little is known regarding the role of the immune system checkpoints in BRCA-mutated cancers, however, data presented at ASCO 2014 by Pockaj et al [10]suggested a high degree of correlation of PD-L1 with lack of BRCA expression, with 7 of 7 BRCA 1 mutated breast cancers overexpressing PD-L1. Data from the Merck/Cedars-Sinai BRCA collaboration in which 30 BRCA-mutated cancers were analyzed indicated a high frequency of PDL-1 expression in BRCA mutated breast cancer.

Based on the observation that genomically unstable malignancies have shown responses to pembrolizumab, the association of PDL-1 expression with likelihood of response, and the preliminary data suggesting a high rate of PDL-1 expression in BRCA-mutated breast cancer, the

trial will evaluate the use of pembrolizumab in addition to olaparib in a population with incurable, advanced breast cancer associated with a germline or somatic BRCA mutation. The genomic instability of BRCA-mutated breast cancer suggests probable increased neoantigen production and antigenicity, and predicts a dependence on immune suppression for carcinogenesis and tumor growth.

2.0 STUDY OBJECTIVES

2.1 Primary Objective

Overall Response Rate (ORR) of pembrolizumab therapy in addition to olaparib therapy in advanced BRCA-mutated or HDR-defect breast cancer, as measured by RECIST 1.1, in patients progressing after prior therapy.

2.2 Secondary Objectives

2.2.1 Progression Free Survival (PFS), as measured by RECIST 1.1, in patients progressing after prior therapy from baseline to the date of the first evidence of progression for up to two years.

2.2.2 Overall survival (OS), from baseline until death for up to two years.

2.2.3 Clinical Benefit Rate (CR+PR+SD), as measured by RECIST 1.1, in patients progressing after prior therapy from baseline for up to two years.

2.2.4 Duration of Response (DOR) for CR and PR, as measured by RECIST 1.1, in patients progressing after prior therapy from baseline for up to two years.

2.3 Exploratory and Correlative Objectives

2.3.1 Correlative Studies

The main objective of the translational research component of the IIT is to obtain biomarker measurements of PD-1 and PD-L1 expressions. Archival tumor samples will be sent to Qualtek Molecular Laboratories for analysis. See Sample Handling Manual.

2.4 Endpoints

Therapy administered until documented progression by RECIST 1.1 criteria or unacceptable toxicity.

This trial is a pilot study to assess the objective response rate with immunotherapy. There are no preliminary statistical assumptions. Stopping rules described in Section 9.

First response assessments at 9 weeks; time interval for trial assessment is typical for time interval for assessment of response to standard of care therapy. Investigational therapy will not preclude subsequent standard of care therapy or subsequent investigational therapy.

3.0 PATIENT ELIGIBILITY

3.1 Inclusion Criteria

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

3.1.2 Be ≥18 years of age on day of signing informed consent

3.1.3 Advanced BRCA-mutated and/or HDR-defect breast cancer progressing on or after prior therapy for metastatic disease or locally advanced disease; Prior therapy is defined as follows: for triple negative breast cancer – progressing after at least 1 line of any prior chemotherapy; for HER2 positive disease must have progressed after at least two HER2 directed therapies in the metastatic setting including ado-trastuzumab emtansine (T-DM1); for hormone receptor positive disease (ER, PR, or both) must have progressed after a CDK4/CDK6 inhibitor plus hormonal therapy**.** Patients with progression within 12 months from previous neoadjuvant or adjuvant treatment could be enrolled in the study as 1st line therapy in metastatic setting.

3.1.4 Measurable disease by RECIST 1.1, with at least one lesion, not previously irradiated, that can be accurately measured at baseline as ≥ 10 mm in the longest diameter (except lymph nodes which must have short axis ≥ 15 mm) with computed tomography (CT) or magnetic resonance imaging (MRI) and which is suitable for accurate repeated measurements. Patients with non-measurable bone metastases in addition to measurable disease are eligible; however patients with non-measurable bone disease as the only site(s) of disease are not eligible.

3.1.5 ECOG 0 or 1

3.1.6 Documented BRCA deleterious germline or somatic mutation ***AND/OR*** HDR-defect.

3.1.7 FFPE tumor tissue available for analysis

3.1.8 Adequate organ function as defined in Table 1

Table 1 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1500/μL
Platelets	≥100 000/μL
Hemoglobin	≥10.0 g/dL or ≥5.6 mmol/L[a], with no blood transfusion in the past 28 days
Renal	
Creatinine OR Measured or calculated[b] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 × ULN OR ≥51 mL/min for participant with creatinine levels >1.5 × institutional ULN
Hepatic	
Total bilirubin	≤1.5 ×ULN OR direct bilirubin ≤ULN for participants with total bilirubin levels >1.5 × ULN

AST (SGOT) and ALT (SGPT)	≤2.5 × ULN (≤5 × ULN for participants with liver metastases)
Coagulation	
International normalized ratio (INR) OR prothrombin time (PT) Activated partial thromboplastin time (aPTT)	≤1.5 × 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 using Cockcroft-Gault equation or based on 24-hour urine.

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

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

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.

3.1.9 Female subjects: Postmenopausal or evidence of non-childbearing status for women of childbearing potential: negative urine or serum pregnancy test within 28 days of study treatment and confirmed prior to treatment on day 1.

Postmenopausal is defined as:

- Amenorrheic for 1 year or more following cessation of exogenous hormonal treatments Luteinizing hormone (LH) and Follicle stimulating hormone (FSH) levels in the post menopausal range for women under 50
- radiation-induced oophorectomy with last menses >1 year ago
- chemotherapy-induced menopause with >1 year interval since last menses
- surgical sterilisation (bilateral oophorectomy or hysterectomy)

3.1.10 Women of childbearing potential and their partners, who are sexually active, must agree to the use of TWO highly effective forms of contraception in combination (as described in Appendix). This should be started from the signing of the informed consent and continue throughout the period of taking study treatment and for at least 1 month after last dose of study drug(s), or they must totally/truly abstain from any form of sexual intercourse (as described in Appendix).

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

3.1.12 Patients must have a life expectancy ≥ 16 weeks

3.2 Exclusion Criteria

3.2.1 Is currently participating or has participated in a study of investigational agent or using an investigational device with 30 days of the first dose of pembrolizumab.

3.2.2 a. Has had prior chemotherapy, targeted small molecule therapy, or radiation therapy within 3 weeks prior to study Day 1

b. Subjects must have recovered (i.e., ≤ Grade 1 or at baseline) from any adverse events due to a previously administered agent. Subjects with ≤ Grade 2 neuropathy are an exception to this criterion and may qualify for the study.

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

3.2.3 Is receiving systemic steroid therapy within three days prior to the first dose of pembrolizumab or receiving any other form of immunosuppressive medication

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

- Subjects with ER+/PR+ disease may be given endocrine therapy.
- Subjects with HER2+ disease will be required to discontinue trastuzumab (Herceptin).

3.2.5 Has participated in another MK03475 trial.

3.2.5.1 Note: Patients with or without prior PARP-inhibitor exposure may be included.

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

3.2.7 Concomitant use of known strong (eg. phenobarbital, enzalutamide, phenytoin, rifampicin, rifabutin, rifapentine, carbamazepine, nevirapine and St John's Wort) or moderate CYP3A inducers (eg. bosentan, efavirenz, modafinil). The required washout period prior to starting olaparib is 5 weeks for enzalutamide or phenobarbital and 3 weeks for other agents.

3.2.8 Major surgery within 2 weeks of starting study treatment and patients must have recovered from any effects of any major surgery.

3.2.9 Has known hypersensitivity to pembrolizumab or any of its excipients

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

3.2.11 Has known history of prior malignancy except if the patient has undergone potentially curative therapy with no evidence of that disease recurrence for 5 years since initiation of that therapy.

3.2.12 Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by MRI for at least four weeks prior to the first dose of pembrolizumab and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are using no steroids for at least three days prior to study medication.

3.2.13 Has evidence of interstitial lung disease or active, non-infectious pneumonitis

3.2.14 Has active tuberculosis

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

3.2.16 Persistent toxicities (>Common Terminology Criteria for Adverse Event (CTCAE) grade 2) caused by previous cancer therapy, excluding alopecia.

3.2.17 Patients with myelodysplastic syndrome/acute myeloid leukaemia or with features suggestive of MDS/AML.

3.2.18 Patients unable to swallow orally administered medication and patients with gastrointestinal disorders likely to interfere with absorption of the study medication.

3.2.19 Patients with a known hypersensitivity to olaparib or any of the excipients of the product.

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

3.2.21 Has a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies). Has known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected).

3.2.22 Has an 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). Subjects with vitiligo or resolved childhood asthma/atopy would be exception to this rule. Subjects that require inhaled steroid or local steroid injections will not be excluded from the study. Subjects with hypothyroidism not from autoimmune disease and stable on hormone replacement will not be excluded from the study. Note: Replacement therapy (eg., thyroxine, insulin, or physiologic

corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.

3.2.23 Has had an allogenic tissue / solid organ transplant.

3.2.24 Previous allogenic bone marrow transplant or double umbilical cord blood transplantation (dUCBT).

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

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

3.2.27 Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the screening visit (Visit 1) through 120 days after the last dose of study treatment.

4.0 TREATMENT PLAN

4.1 Treatment Dosage and Administration

This is an open-label, single-arm pilot study in 20 subjects with advanced BRCA mutation or HDR-defect associated breast cancer having progressed through standard first line therapy.

The study participation is up to 35 administrations of pembrolizumab (approximately two years).

Pembrolizumab and olaparib will be supplied by Merck.

Pembrolizumab will be administered at a dose of 200mg as a 30 minute IV infusion Q3W. Effort should be made to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min).

Olaparib 300mg will be self-administered orally twice daily. The dose of olaparib used in this study is 300 mg twice daily which is the currently approved dose. Subjects will complete a compliance diary throughout the study treatment period. Olaparib tablets should be taken at the same time each day, approximately 12 hours apart with one glass of water. The tablets should be swallowed whole and not chewed, crushed, dissolved or divided. Olaparib tablets can be taken with or without food. Each container will be labelled in accordance with Good Manufacturing Practice (GMP) Annex 13 and per country regulatory requirement. If vomiting occurs shortly after the olaparib tablets are swallowed, the dose should only be replaced if all of the intact tablets can be seen and counted. Should any patient enrolled on the study miss a scheduled dose for whatever reason (e.g., as a result 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.

The Pharmacy Manual contains specific instructions for pembrolizumab dose calculation, reconstitution, preparation of the infusion fluid, and administration.

Table 2. Trial Intervention

Drug	Dose/Potency	Dose/	Route of	Regimen/ Treatment

		Frequency	Administration	Period
Pembrolizumab	200 mg	Q3W	IV infusion	Day 1 of each cycle
Olaparib	300mg	BID	PO	Continuous; dispensed each cycle day 1 (each cycle=3 weeks)

4.1.1 Meals and dietary restrictions

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

4.2 Toxicities, Dosing Delays, and Dose Modifications

4.2.1 Pembrolizumab

If a dose of pembrolizumab is withheld for toxicity, then subjects may resume dosing with pembrolizumab if that is appropriate at their next scheduled appointment or when toxicity has improved as described below.

Pembrolizumab will be withheld for drug-related Grade 4 hematologic toxicities, nonhematological toxicity ≥ Grade 3 including laboratory abnormalities, and severe or life-threatening adverse events.

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

Attribution of Toxicity:
When study interventions are administered in combination, attribution of an adverse event to a single component is likely to be difficult. Therefore, while the investigator may attribute a toxicity event to the combination, to olaparib alone, or to pembrolizumab alone, for adverse events listed in Table 3, both interventions must be held according to the criteria in Table 3 Dose Modification and Toxicity Management Guidelines for Immune-Related Adverse Events Associated with Pembrolizumab.

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

Restarting Study Interventions:
Participants may not have any dose modifications (no change in dose or schedule) of pembrolizumab in this study, as described in Table 3.
If the toxicity does not resolve or the criteria for resuming treatment are not met, the participant must be discontinued from all study interventions.
If the toxicities do resolve and conditions are aligned with what is defined in Table 3, the combination of olaparib and pembrolizumab may be restarted at the discretion of the investigator. In these cases where the toxicity is attributed to the combination or to

olaparib alone, re-initiation of pembrolizumab as a monotherapy may be considered at the principal investigator's discretion.

Dosing Interruptions:
Dosing interruptions are permitted in the case of medical / surgical events or logistical reasons not related to study therapy (e.g., elective surgery, unrelated medical events, patient vacation, and/or holidays). Subjects should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the Sponsor. The reason for interruption should be documented in the patient's study record.

Table 3: Dose Modification and Toxicity Management Guidelines for Immune-related AEs Associated with Pembrolizumab monotherapy and IO combinations

General instructions:

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

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper • Add prophylactic antibiotics for opportunistic infections	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment
	Recurrent Grade 2, Grade 3 or 4	Permanently discontinue		
Diarrhea/Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
	Recurrent Grade 3 or Grade 4	Permanently discontinue		and ileus) • Participants with ≥Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion
AST or ALT Elevation or Increased Bilirubin	Grade 2 [a]	Withhold	• Administer corticosteroids (initial dose of 0.5 to 1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable)
	Grade 3 [b] or 4 [c]	Permanently discontinue	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	
T1DM or Hyperglycemia	New onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold [d]	• Initiate insulin replacement therapy for participants with T1DM • Administer antihyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue [d]		
Hyperthyroidism	Grade 2	Continue	• Treat with nonselective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders
	Grade 3 or 4	Withhold or permanently discontinue [d]		
Hypothyroidism	Grade 2, 3 or 4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care	• Monitor for signs and symptoms of thyroid disorders
Nephritis: grading according to increased creatinine or acute kidney injury	Grade 2	Withhold	• Administer corticosteroids (prednisone 1 to 2 mg/kg or equivalent) followed by taper	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Neurological Toxicities	Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 2, 3 or 4	Permanently discontinue		

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Confirmed SJS, TEN, or DRESS	Permanently discontinue		
All Other irAEs	Persistent Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 3	Withhold or discontinue based on the event [e]		
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

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

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

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

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

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

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

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

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

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

Table 4 Pembrolizumab Infusion Reaction Dose modification and Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g. from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the participant should be premedicated for the next scheduled dose. **Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment**	Participant may be premedicated 1.5h (± 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).
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: Epinephrine** IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Oxygen Pressors Corticosteroids Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. **Participant is permanently discontinued from further study drug treatment.**	No subsequent dosing
Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE) at http://ctep.cancer.gov		

4.2.2 Olaparib Dose Reductions

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

Table 5 Dose reductions for study treatment to manage adverse events

Initial Dose	Following re-challenge post interruption: Dose reduction 1	Dose reduction 2
300 mg twice daily	250 mg twice daily	200 mg twice daily

Table 6 Dose reduction for olaparib if patient develops moderate renal impairment

Initial Dose	Moderate renal impairment (calculated creatinine clearance by Cockcroft -Gault equation or based on a 24 hour urine test between 31 and 50 ml/min): Dose reduction
300 mg twice daily	200 mg twice daily

Table 7 Dose reductions for study treatment if patient has to start taking a strong or moderate CYP3A inhibitor

Initial Dose	Strong CYP3A inhibitor	Moderate CYP3A inhibitor
300 mg twice daily	100 mg twice daily	150 mg twice daily

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. Olaparib 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 Olaparib should be discontinued.
Once Olaparib dose is reduced, escalation is not permitted (except following concomitant treatment with CYP3A4 inhibitors).

When Olaparib dose reduction is necessary patients will take one 150 mg tablet and one 100 mg tablet twice daily or two x 100 mg tablet twice daily, or one 150 mg tablet twice daily or one 100 mg tablet twice daily.

4.2.3 Olaparib Management of Adverse Events

4.2.3.1 Management of haematological toxicity

Management of anaemia

Table 8 Management of anaemia

Haemoglobin	Action to be taken
Hb < 10 *but* **≥ 8 g/dl (CTCAE Grade 2)**	**First occurrence:** Give appropriate supportive treatment and investigate causality. Investigator judgement to continue olaparib with supportive treatment (eg transfusion) *or* interrupt dose for a maximum of 4 weeks. Olaparib can be restarted if Hb has recovered to > 9g/dl. **Subsequent occurrences:** If Hb**< 10** *but* **≥ 9 g/dl** investigator judgement to continue olaparib with supportive treatment (eg transfusion) *or* dose interrupt (for max of 4 weeks) and upon recovery dose reduction may be considered (to **250 mg twice daily** as a first step and to **200 mg twice daily** as a second step). If Hb**< 9** *but* **≥ 8 g/dl**, dose interrupt (for max of 4 weeks) until Hb ≥ 9 g/dl and upon recovery dose reduction may be considered (to **250 mg twice daily** as a first step and to **200 mg twice daily** as a second step).
Hb < 8 g/dl (CTCAE Grade 3)	Give appropriate supportive treatment (e.g. transfusion) and investigate causality. *Interrupt Olaparib for* a maximum of 4 weeks until improved to Hb ≥ 9 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.

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

Management of neutropenia, leukopenia and thrombocytopenia

Table 9 Management of neutropenia, leukopenia and thrombocytopenia

Toxicity	Study treatment dose adjustment
CTCAE Grade 1-2	Investigator judgement to continue treatment or if dose interruption, this should be for a maximum of 4 weeks; appropriate supportive treatment and causality investigation
CTCAE Grade 3-4	Dose interruption until recovered to CTCAE 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

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 CTC 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, olaparib should be stopped and appropriate management including G-CSF should be given according to local hospital guidelines. Please note that G-CSF should not be used within at least 24 h (7 days for pegylated G-CSF) of the last dose of study treatment unless absolutely necessary.
Platelet transfusions, if indicated, should be done according to local hospital guidelines.

For cases where patients develop prolonged haematological toxicity (≥2 week interruption/delay in olaparib due to CTC grade 3 or worse), refer to guidance later in this section for the management of this.

Management of prolonged haematological toxicities while on study treatment

If a patient develops prolonged haematological toxicity such as:
≥2 week interruption/delay in olaparib due to CTC grade 3 or worse anaemia and/or development of blood transfusion dependence

≥2 week interruption/delay in olaparib due to CTC grade 3 or worse neutropenia (ANC < 1 x 10^9/L)

≥2 week interruption/delay in olaparib due to CTC grade 3 or worse thrombocytopenia and/or development of platelet transfusion dependence (Platelets < 50 x 10^9/L)

Check weekly differential blood counts including reticulocytes and peripheral blood smear. If any blood parameters remain clinically abnormal after 4 weeks of dose interruption, the patient should be referred to haematologist for further investigations. Bone marrow analysis and/or blood cytogenetic analysis should be considered at this stage according to standard haematological practice. Olaparib should be discontinued if blood counts do not recover to CTC 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 Merck. Olaparib treatment should be discontinued if patient's diagnosis of MDS and/or AML is confirmed.

4.2.3.2 Management of non-haematological toxicity

Repeat dose interruptions are allowed as required, for a maximum of 4 weeks on each occasion. If the interruption is any longer than this the study monitor must be informed. Where toxicity reoccurs following re-challenge with olaparib, and where further dose interruptions are considered inadequate for management of toxicity, then the patient should be considered for dose reduction or must permanently discontinue olaparib.
Olaparib can be dose reduced to 250 mg twice daily as a first step and to 200 mg twice daily as a second step. Treatment must be interrupted if any NCI-CTCAE grade 3 or 4 adverse event occurs which the investigator considers to be related to administration of study treatment.

Management of new or worsening pulmonary symptom
If new or worsening pulmonary symptoms (e.g., dyspnoea) or radiological abnormalities occur in the absence of a clear diagnosis, an interruption in study treatment dosing is recommended and further diagnostic workup (including a high resolution CT scan) should be performed to exclude pneumonitis.
Following investigation, if no evidence of abnormality is observed on CT imaging and symptoms resolve, then study treatment can be restarted, if deemed appropriate by the investigator. If significant pulmonary abnormalities are identified, these need to be discussed with the Study Physician.

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

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.

Interruptions for intercurrent non-toxicity related events
Olaparib dose interruption for conditions other than toxicity resolution should be kept as short as possible.

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

Olaparib should be stopped at least 3 days prior to planned surgery. After surgery study treatment can be restarted when the wound has healed. No stoppage of study treatment is required for any needle biopsy procedure.
Study treatment should be discontinued for a minimum of 3 days before a patient undergoes radiation treatment. Study treatment should be restarted within 4 weeks as long as any bone marrow toxicity has recovered.
Because the AEs related to olaparib may include asthenia, fatigue and dizziness, patients should be advised to use caution while driving or using machinery if these symptoms occur.

Table 10 Dose reductions for study treatment

Initial Dose	Following re-challenge post interruption: Dose reduction 1	Dose reduction 2
300 mg twice daily	250 mg twice daily	200 mg twice daily

4.2.3.3 Renal impairment

If subsequent to study entry and while still on study therapy, a patient's estimated CrCl falls below the threshold for study inclusion (≥51 ml/min), retesting should be performed promptly.
A dose reduction is recommended for patients who develop moderate renal impairment (calculated creatinine clearance by Cockcroft-Gault equation or based on a 24 hour urine test of between 31 and 50 ml/min) for any reason during the course of the study: the dose of olaparib should be reduced to 200 mg twice daily.

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

4.3 Concomitant Medications/Treatments

4.3.1 Acceptable Concomitant Medications

All treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. The use of any natural/herbal products or other traditional remedies should be discouraged, but use of these products, as well as any medication or vaccine including over-the-

counter or prescription medicines, vitamins, and/or herbal supplements that the patient is receiving at the time of enrolment or receives during the study must be recorded along with reason for use, dates of administration including start and end dates, dosage information including dose and frequency. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date will also be included on the CRF.

Anti-emetics/Anti-diarrhoeals
Should a patient develop nausea, vomiting and / or diarrhoea, then these symptoms should be reported as AEs (see section 8.3) and appropriate treatment of the event given.

Subjects with ER+/PR+ disease may be given endocrine therapy.

Specifically, subjects using bisphosphonates or anti-RANKL mAb who were receiving this medication prior to study start, may continue receiving the medication during the study. However, a need to initiate this therapy during the conduct of this trial will be the equivalent of clinical disease progression and the subject must discontinue study treatment.

All concomitant medications received within 30 days before the first dose of pembrolizumab through the Safety Follow-up Visit should be recorded. After the Safety Follow-up Visit record all medications taken for SAEs and ECIs as defined in Section 6.3.2.

4.3.2 Prohibited Concomitant Medications

Subjects are prohibited from receiving the following therapies during the Screening, Treatment and Second Course Phases of this trial (unless otherwise noted below):

- Antineoplastic systemic chemotherapy or biological therapy not specified in this protocol.
- Immunotherapy not specified in this protocol
    - Subjects with HER2+ disease will be required to discontinue trastuzumab (Herceptin).
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab
- Non-palliative radiation therapy (radiation that's considered palliative in nature as determined by treating investigator is allowed).
- Live vaccines or live-attenuated vaccines within 30 days prior to the first dose of pembrolizumab and while participating in the trial. Administration of killed vaccines is allowed.
- Initiation of bisphosphonate or anti-RANKL mAb (Treatment and Second Course Phases).

Subjects who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the trial. Subjects may receive other medications that the investigator deems to be medically necessary.

Restricted concomitant medications

Medication/class of drug:	Usage (including limits for duration permitted and special situations in which it's allowed):

Restricted concomitant medications

Medication/class of drug:	Usage (including limits for duration permitted and special situations in which it's allowed):
Strong CYP3A inhibitors: itraconazole, telithromycin, clarithromycin, boosted protease inhibitors, indinavir, saquinavir, nelfinavir, boceprevir, telaprevir Moderate CYP3A inhibitors: ciprofloxacin, erythromycin, diltiazem, fluconazole, verapamil	Strong or moderate CYP3A inhibitors should not be taken with *olaparib*. If there is no suitable alternative concomitant medication then the dose of *olaparib* should be reduced for the period of concomitant administration. The dose reduction of *olaparib* should be recorded in the CRF with the reason documented as concomitant CYP3A inhibitor use. • Strong CYP3A inhibitors – reduce the dose of *olaparib* to 100 mg twice daily 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 150 mg twice daily for the duration of concomitant therapy with the moderate inhibitor and for 3 half lives afterwards. • After the washout of the inhibitor is complete, the *olaparib* dose can be re-escalated.
Strong inducers: phenobarbital, phenytoin, rifampicin, rifabutin, rifapentine, carbamazepine, nevirapine, enzalutamide and St John's Wort Moderate CYP3A inducers: bosentan, efavirenz and modafinil	Strong or moderate CYP3A inducers should not be taken with *olaparib*. If the use of any strong or moderate CYP3A inducers are considered necessary for the patient's safety and welfare this could diminish the clinical efficacy of olaparib. If a patient requires use of a strong or moderate CYP3A inducer then they must be monitored carefully for any change in efficacy of *olaparib.*

Restricted concomitant medications

Medication/class of drug:	Usage (including limits for duration permitted and special situations in which it's allowed):
CYP3A4 substrates: hormonal contraceptive, simvastatin, cisapride, cyclosporine, ergot alkaloids, fentanyl, pimozide, sirolimus, tacrolimus and quetiapine CYP2B6 substrates: bupropion, efavirenz OATP1B1substrates: bosentan, glibenclamide, repaglinide, statins and valsartan OCT1, MATE1 and MATE2K substrates: metformin OCT2 substrates: serum creatinine OAT3 substrates: furosemide, methotrexate	Effect of olaparib on other drugs Based on limited *in vitro* data, olaparib may increase the exposure to substrates of CYP3A4, OATP1B1, OCT1, OCT2, OAT3, MATE1 and MATE2K. Based on limited *in vitro* data, olaparib may reduce the exposure to substrates of 2B6. Caution should be observed if substrates of these isoenzymes or transporter proteins are co-administered.
Anticoagulant therapy	Patients who are taking warfarin may participate in this trial; however, it is recommended that international normalised ratio (INR) be monitored carefully at least once per week for the first month, then monthly if the INR is stable. Subcutaneous heparin and low molecular weight heparin are permitted.
Palliative radiotherapy	Palliative radiotherapy may be used for the treatment of pain at the site of bony metastases that were present at baseline, provided the investigator does not feel that these are indicative of clinical disease progression during the study period. Study treatment should be discontinued for a minimum of 3 days before a patient undergoes therapeutic palliative radiation treatment. Study treatment should be restarted within 4 weeks as long as any bone marrow toxicity has recovered.
Administration of other anti-cancer agents	Patients must not receive any other concurrent anti-cancer therapy, including investigational agents, while on study treatment. Patients may continue the use of bisphosphonates or denosumab for bone disease and corticosteroids for the symptomatic control of brain metastases provided the dose is stable before and during the study and they were started at least 4 weeks prior to beginning study treatment.

4.4 Supportive Care Guidelines

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of adverse events with potential immunologic etiology are outlined below and in greater detail in the ECI guidance document. Where appropriate, these guidelines include the use of oral or intravenous treatment with corticosteroids as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to Pembrolizumab.

Note: if after the evaluation the event is determined not to be related, the investigator is instructed to follow the ECI reporting guidance but does not need to follow the treatment guidance (as outlined in the ECI guidance document). Refer to Section 4.2.1 for dose modification.
It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event. Suggested conditional procedures, as appropriate, can be found in the ECI guidance document.

4.5 Duration of Therapy

Patients will continue with pembrolizumab until disease progression or unacceptable toxicity, or until completion of 35 treatments of pembrolizumab (approximately 2 years), as long as in the Investigator's opinion they are benefiting from treatment and they do not meet any other discontinuation criteria. Once patients have been discontinued from study treatment, other treatment options (including compassionate use) will be at the discretion of the investigator. Subjects will receive olaparib according to the FDA approved package insert until disease progression or unacceptable toxicity.

In patients with initial disease progression substantiated by radiographic imaging per RECIST 1.1, study treatment may continue until repeat imaging is conducted, at least 4 weeks and no later than 8 weeks later, under the following conditions:

- No worsening of ECOG Performance Status
- No clinically relevant increases in disease-related symptoms thought to be associated with disease progression
- No requirement for intensified management of disease-related symptoms exists, including increased analgesia, radiotherapy, or other palliative care.

Disease progression can also be confirmed histologically, cytologically, or surgically, or by physical examination or other clinical signs, per PI discretion.

4.6 Duration of Follow Up

Primary and secondary response objectives will be met with approximately 1 month end of study follow-up for subjects discontinuing therapy due to progression. Subjects who discontinue trial treatment for a reason other than disease progression will move into the Follow-Up Phase and should be assessed every 12 weeks (56 ± 7 days) by radiologic imaging to monitor disease status, per standard of care for up to two years of total study participation. Every effort should be made to collect information regarding disease status until the start of new anti-neoplastic therapy, disease progression, death, or at end of the study.

4.7 Removal of Patients from Protocol

Patients will be removed from the study when any of the criteria listed in Section 5.15 apply. Notify the Principal Investigator, and document the reason for study removal and the date the patient was removed in the Case Report Form. The patient should be followed-up per protocol.

4.8 Subject Evaluability and Replacement Guidelines

- Subjects who withdraw from the study treatment prior to starting study intervention will be replaced.
- Subjects who receive at least one dose of study treatment (pembrolizumab and olaparib) will be included in the safety analysis.
- Subjects who do not complete at least 6 weeks (2 cycles) of study treatment (pembrolizumab and olaparib) will not be evaluable for efficacy and will be replaced.

5.0 STUDY PROCEDURES

Assessments performed exclusively to determine eligibility for this study will be done only after obtaining informed consent. Assessments performed for clinical indications (not exclusively to determine study eligibility) may be used for baseline values even if the studies were done before informed consent was obtained.

All screening procedures must be performed within six weeks prior to C1D1 unless otherwise stated.

Note: It is estimated that up to 100-200 patients may be screened on this protocol to determine eligibility based on HDR status.

5.1 Informed Consent

Consent must be documented by the subject's dated signature or by the subject'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 subject before participation in the trial.

The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the subject must receive the IRB/ERC's approval/favorable opinion in advance of use. The subject or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject'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 subject's dated signature or by the subject's legally acceptable representative's dated signature.

5.2 Tempus HRD

Tempus HRD will be used to determine HDR status, for patients who do not otherwise qualify for the study based on BRCA status; Tempus HRD testing will not be performed on patients who qualify for the study based on BRCA status.

Archival tumor tissue samples (FFPE blocks or slides), as well as a normal sample type [blood (preferred), FFPE adjacent normal tissue, or saliva] will be sent to Tempus for testing. Refer to the Lab Manual and Tempus Specimen Guidelines.

In addition, de-identified clinical data elements will be shared with Tempus, as specified in the master agreement.

5.3 Pregnancy Test

Female subjects of childbearing potential should have a negative urine or serum pregnancy prior to study registration and re-tested within 72 hours prior to receiving the first dose of pembrolizumab. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

5.4 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. Demographic information will be collected at screening and will include ethnicity, age, and gender.

5.5 Physical Exam

The investigator or qualified designee will perform a full or directed physical exam as clinically indicated. Clinically significant abnormal findings should be recorded as medical history. The time points for physical exam are outlined in Section 5.14. After the first dose of pembrolizumab, new clinically significant abnormal findings should be recorded as AEs.

5.6 Vital signs

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

5.7 ECOG Performance Status

The investigator or qualified designee will assess ECOG status at screening, prior to the administration of each dose of trial treatment and during the Follow-up as specified in the Trial Flow Chart.

5.8 Laboratory Safety Evaluations

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

Laboratory tests for screening should be performed within 10 days prior to the first dose of pembrolizumab. 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.

Hematology	Chemistry	Other
Hemoglobin	Albumin	Triiodothyronine (T3)
Platelets	Alkaline phosphatase	Free thyroxine (FT4)
WBC (total and differential)	Alanine aminotransferase	Thyroid stimulating hormone

	(ALT)	(TSH)
Absolute Neutrophil Count	Aspartate aminotransferase (AST)	Coagulation: PT, INR, aPTT
Absolute Lymphocyte Count	Creatinine or calculated creatinine clearance (CrCl)	
	Calcium	
	Glucose	
	Potassium	
	Sodium	
	Total Bilirubin	
	Blood Urea Nitrogen	

5.9 EKG

5.10 Blood Tumor Markers

Serum tumor markers such as CA 27-29, CEA and CA-125 may be measured at the discretion of the investigator as a supplement to clinical parameters for monitoring of response.

5.11 Archival Tumor Tissue Collection

Archival tumor tissue will be collected for Exploratory Studies (see Section 8). This tissue from a prior biopsy or surgery will also be collected for routine analysis if confirmation of diagnosis or histologic subtype is uncertain from available data.

5.12 Tumor Assessments

Tumor assessments will be conducted according to protocol timeline at 9 week intervals, with CT, MRI or other appropriate imaging, as well as physical exam and clinical measurements as appropriate while on study drug during Year 1. Tumor imaging will be obtained every 12 weeks after drug discontinuation, per standard of care, or during Year 2 of study treatment. RECIST version 1.1 will be used in this study for assessment of tumor response. While either CT or MRI may be utilized, as per RECIST 1.1, CT is the preferred imaging technique in this study.

Bone scans will be performed at screening for any subject with known bone metastases and/or new bone pain and musculoskeletal complaints. During the study, bone scans will be performed as needed for evaluation of worsening and/or new bone pain and musculoskeletal complaints or if the site believes they have attained a Complete Response. If a subject has no known metastatic disease in the bone or active symptoms, a bone scan at baseline is not needed. A bone scan can be obtained at follow up if there are new symptoms of bone pain.

5.13 Adverse Event Assessment

Adverse event assessment will be undertaken at every clinical visit. See 5.14.

An investigator who is a qualified physician will evaluate all adverse events according to the NCI Common Terminology for Adverse Events (CTCAE), version 4.0. Any adverse event which changes CTCAE grade over the course of a given episode will have each change of grade recorded on the adverse event case report forms/worksheets.

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

5.14 Concomitant Medications

Concomitant Medications will be assessed at every clinical visit. See 5.14.

5.15 Time and Events Table

Procedure	Screening (Within 6 weeks of Day 1)	Treatment Phase (+/- 3 days)[3]											End of Treatment[4]	SOC Follow-up[5]
		C1 D1	C1 D8	C1 D15	C2 D1	C2 D8	C3 D1	C4 D1	C5 D1	C6 D1	Even Cycles	Odd Cycles	30-days after drug discontinuation, +/- 7 days	Every 12 Weeks
Informed Consent[1]	X													
Tempus HRD[11]	X													
Physical Exam (includes Medical history)	X	X	X	X	X		X	X	X	X	X	X	X	X
Vitals[2]	X	X	X	X	X		X	X	X	X	X	X	X	X
ECOG Performance Status	X	X			X		X	X	X	X	X	X	X	X
Hematology[8]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chemistry[8]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Tumor markers (CA2729, CEA, CA-125)	as per standard of care, at the investigator's discretion													
T3 Free, T4 Free, TSH[8]	X				X			X		X	X		X	
Coagulation (PT, INR, aPTT)	X[8]													
Urine or serum pregnancy test	X[9]													
EKG	X													
Archival Tumor Tissue Collection	X[10]													
CT Scan (Chest, Abdomen, Pelvis) and/or MRI	X		As clinically indicated (or every 9 weeks for Response assessment)											X
Whole body Bone Scan	X		As clinically indicated											

Procedure	Screening (Within 6 weeks of Day 1)	Treatment Phase (+/- 3 days)[3]											End of Treatment[4]	SOC Follow-up[5]
		C1 D1	C1 D8	C1 D15	C2 D1	C2 D8	C3 D1	C4 D1	C5 D1	C6 D1	Even Cycles	Odd Cycles	30-days after drug discontinuation, +/- 7 days	Every 12 Weeks
Adverse Event Assessment	X	X		X	X		X	X	X	X	X	X	X[6]	X[6]
Concomitant Medications	X	X		X	X		X	X	X	X	X	X	X	X
Pembrolizumab Administration		X			X		X	X	X	X	X	X		
Olaparib Administration and Olaparib Compliance Diary		Daily[7]												

[1]Informed consent may be obtained within 6 weeks of Cycle 1, Day 1

[2]Vital signs to include temperature, pulse, respiratory rate, weight, and blood pressure. Height will be measured at Screening only.

[3]Study treatment is up to 35 administrations of pembrolizumab (approximately two years).

[4]If subject discontinues drug due to progression, the End of Treatment visit (30 days after study treatment discontinuation, +/- 7 days) will end their participation in the study and will not be followed thereafter.

[5]Subjects who discontinue trial treatment for a reason other than disease progression will move into the Follow-Up Phase and should be assessed every 12 weeks (56 ± 7 days) by radiologic imaging to monitor disease status, per standard of care for up to two years of total study participation.

[6]*SAEs and ECIs* should be reported for 90 days after last pembrolizumab dose or until new anticancer treatment is initiated, but for a minimum of 30 days, whichever occurs first.

[7]Olaparib will be dispensed each cycle day 1 (each cycle=3 weeks). Subjects will be given an olaparib dosing diary at Cycle 1 Day 1, and at Day 1 of each subsequent cycle while taking olaparib. The completed diary will be collected at the next cycle Day 1. Olaparib dosing must begin within 3 days of pembrolizumab C1D1.

[8]Laboratory tests for screening should be performed within 10 days prior to the first dose of pembrolizumab. 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.

[9] Female subjects of childbearing potential should have a negative urine or serum pregnancy prior to study registration and re-tested within 72 hours prior to receiving the first dose of pembrolizumab. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

[10]The pre-treatment archival tumor tissue sample for correlative studies may be sent to QualTek any time after eligibility verification.

[11] Tempus testing will be performed only on patients who do not otherwise qualify based on BRCA status. Archival tumor tissue plus a normal matching sample (blood preferred) will be collected and shipped to Tempus. De-identified clinical data elements will be shared with Tempus as specified in the master agreement (may be sent after screening).

5.16 Removal of Subjects from Study

Patients can be taken off the study treatment and/or study at any time at their own request, or they may be withdrawn at the discretion of the investigator for safety, behavioral or administrative reasons. The reason(s) for discontinuation will be documented and may include:

5.16.1 Patient voluntarily withdraws from treatment (follow-up permitted);

5.16.2 Patient withdraws consent (termination of treatment and follow-up);

5.16.3 Patient is unable to comply with protocol requirements;

5.16.4 Patient experiences toxicity that makes continuation in the protocol unsafe;

5.16.5 Treating physician judges continuation on the study would not be in the patient's best interest;

5.16.6 Patient becomes pregnant (pregnancy to be reported along same timelines as a serious adverse event).

6.0 ADVERSE EVENTS

6.1 Definitions

6.1.1 Definition of Adverse Event

Adverse Event (AE or Adverse Experience): Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Therefore, an AE can be **ANY** unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product (attribution of unrelated, unlikely, possible, probable, or definite). AE's will be collected once the consent is signed and treatment is initiated.

6.1.2 Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be recorded as such on the Adverse Event case report forms/worksheets and reported within 2 working days from time of PI acknowledgment to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 661-6229)

Events of clinical interest for this trial include:

1. an overdose of pembrolizumab that is not associated with clinical symptoms or abnormal laboratory results. For purposes of this study, an overdose of pembrolizumab will be defined as any dose of 1,000 mg or greater (≥5 times the indicated dose). No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated. If an adverse event(s) is associated with ("results from") the overdose of a Merck product, the adverse event(s) is reported as a serious adverse event, even if no other seriousness criteria are met.
2. an elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

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

ECIs (both non-serious and serious adverse events) identified in this guidance document from the date of first dose through 90 days following cessation of treatment, or 30 days after the initiation of a new anticancer therapy, whichever is earlier, need to be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 661-6229), regardless of attribution to study treatment, consistent with standard SAE reporting guidelines.

Subjects should be assessed for possible ECIs prior to each dose. Lab results should be evaluated and subjects should be asked for signs and symptoms suggestive of an immune-related event. Subjects who develop an ECI thought to be immune-related should have additional testing to rule out other etiologic causes. If lab results or symptoms indicate a possible immune-related ECI, then additional testing should be performed to rule out other etiologic causes. If no other cause is found, then it is assumed to be immune-related.

6.1.2.1 Olaparib Overdose

There is currently no specific treatment in the event of overdose with olaparib and possible symptoms of overdose are not established.

Olaparib must only be used in accordance with the dosing recommendations in this protocol. Any dose or frequency of dosing that exceeds the dosing regimen specified in this protocol should be reported as an overdose. The maximum tolerated dose is 300mg twice daily (tablet).

Adverse reactions associated with overdose should be treated symptomatically and should be managed appropriately.

For overdoses associated with a SAE, the standard reporting timelines apply, see Section 6.4. For other overdoses, reporting must occur within 30 days.

6.1.3 Severity of Adverse Events

All non-hematologic adverse events will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. The CTCAE v4 is available at http://ctep.cancer.gov/reporting/ctc.html

If no CTCAE grading is available, the severity of an AE is graded as follows:

- Mild (grade 1): the event causes discomfort without disruption of normal daily activities.
- Moderate (grade 2): the event causes discomfort that affects normal daily activities.
- Severe (grade 3): the event makes the patient unable to perform normal daily activities or significantly affects his/her clinical status.
- Life-threatening (grade 4): the patient was at risk of death at the time of the event.
- Fatal (grade 5): the event caused death.

6.1.4 Serious Adverse Events

A “serious” adverse event is defined in regulatory terminology as any untoward medical occurrence that:

- **Results in death.**
  If death results from (progression of) the disease, the disease should be reported as event (SAE) itself.

- **Is life-threatening.**
  (the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe).

- **Requires in-patient hospitalization or prolongation of existing hospitalization for ≥ 24 hours.**

- **Results in persistent or significant disability or incapacity.**

- **Is a congenital anomaly/birth defect**

- **Is an important medical event**

Any event that does not meet the above criteria, but that in the judgment of the investigator jeopardizes the patient, may be considered for reporting as a serious adverse event. The event may require medical or surgical intervention to prevent one of the outcomes listed in the definition of “Serious Adverse Event”.

For example: allergic bronchospasm requiring intensive treatment in an emergency room or at home; convulsions that may not result in hospitalization; development of drug abuse or drug dependency.

Pregnancy: If a female subject or male subject’s female partner inadvertently becomes pregnant while on treatment with pembrolizumab, the subject will immediately be removed from the study. The site will contact the subject at least monthly and document the subject’s status until the pregnancy has been

completed or terminated. The outcome of the pregnancy will be reported to the IRB and to Merck within 10 days of the PI becoming aware of the outcome. 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 PI upon learning of the event, will report to Merck.

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 the IRB.

6.2 Steps to Determine If an Adverse Event Requires Expedited Reporting

Step 1: Identify the type of adverse event using the NCI Common Terminology Criteria for Adverse Events (CTCAE v4).

Step 2: Grade the adverse event using the NCI CTCAE v4.

Step 3: Determine whether the adverse event is related to the protocol therapy
Attribution categories are as follows:

- Definite – The AE *is clearly related* to the study treatment.
- Probable – The AE *is likely related* to the study treatment.
- Possible – The AE *may be related* to the study treatment.
- Unrelated – The AE *is clearly NOT related* to the study treatment.

Note: This includes all events that occur within 30 days of the last dose of protocol treatment. Any event that occurs more than 30 days after the last dose of treatment and is attributed (possibly, probably, or definitely) to the agent(s) must also be reported accordingly. SAEs and ECIs should be reported for 90 days after last pembrolizumab dose or until new anticancer treatment is initiated, but for a minimum of 30 days, whichever occurs first.

Step 4: Determine the prior experience of the adverse event.
Expected events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered unexpected, for expedited reporting purposes only, when either the type of event or the severity of the event is not listed in the current known adverse events listed in:

- the current known adverse events listed this protocol;
- the drug package insert; and/or
- the current Investigator's Brochure

6.3 Data Collection Procedures for Adverse Events

The principal investigator is responsible for evaluating all adverse events, obtaining supporting documents, and determining that documentation of the event is adequate. He/she is responsible for determining the seriousness, severity, and relationship of the adverse event to the investigational drug. The principal investigator may delegate these duties to sub-investigators and must assure that these sub-investigators are qualified to perform these duties under the supervision of the principal investigator. All adverse events will be documented in the subject's source and recorded on Case Report Form(s).

The term of the adverse event should reflect the diagnosis rather than its symptoms, when available. In the event of death, the cause of death should be recorded as the adverse

event. The detailed description of the event will include appropriately graded severity of the adverse event and its relationship to the study drug.

"Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. However, the signs and symptoms and/or clinical sequelae resulting from lack of efficacy will be reported if they fulfill the definition of an AE or SAE.

Events that **do not** meet the definition of an AE include:

Any clinically significant abnormal laboratory finding or other abnormal safety assessments that is associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition.

Abnormal laboratory findings deemed by the investigator as not clinically significant.

The disease/disorder being studied, or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition

Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that leads to the procedure is an AE

Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)

Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen

All patients experiencing an adverse event will be monitored until:

- The adverse event resolves or the symptoms or signs that constitute the adverse event return to baseline;
- Any abnormal laboratory values have returned to baseline[1];
- There is a satisfactory explanation other than the study drug for the changes observed; or
- Death.

Serious adverse events, occurring after the informed consent is signed but prior to the initial dose of the investigational product will be collected as part of the subject's medical history/baseline symptoms but will only be reportable if they are considered by the Investigator to be causally related to required research procedures.

SAEs and ECIs should be reported for 90 days after last pembrolizumab dose or until new anticancer treatment is initiated, but for a minimum of 30 days, whichever occurs first.

[1] An abnormal laboratory value is considered to be an AE if the abnormality: 1) results in discontinuation from the study; 2) requires treatment, modification/ interruption of IP dose, or any other therapeutic intervention; or 3) is judged to be of significant clinical importance. Regardless of severity grade, only laboratory abnormalities that fulfill a seriousness criterion need to be documented as a serious adverse event.

If a laboratory abnormality is one component of a diagnosis or syndrome, then only the diagnosis or syndrome should be recorded on the AE page/screen of the eCRF. If the abnormality was not a part of a diagnosis or syndrome, then the laboratory abnormality should be recorded as the AE.

Non-serious adverse events (AEs) will be collected throughout the treatment period through the End of Treatment assessment 30 days after removal from treatment. Patients removed from treatment for unacceptable adverse events will be followed until resolution or stabilization of the adverse event. Events occurring during this period must be followed until resolution or death unless in the Investigator's opinion, the condition is unlikely to resolve due to the patient's underlying disease. After the End of Treatment assessment, any adverse event documented in the subject's medical record as being at least possibly related to study intervention will also be recorded in the Case Report Form.

SAEs must be reported to oversight agencies as described below.

6.4 Reporting Requirements for Adverse Events

6.4.1 Expedited Reporting to PI

The Principal Investigator must be notified within 24 hours of learning of any serious adverse events, regardless of attribution, occurring during the study or within 30 days of the last administration of the study drug. SAEs and ECIs should be reported for 90 days after last pembrolizumab dose or until new anticancer treatment is initiated, but for a minimum of 30 days, whichever occurs first.

Phone Number for Expedited Reporting:
310-248-6733

Alternate Phone Number for Expedited Reporting:
310-423-1188

6.4.2 Reporting to DSMC

Serious Adverse Event deemed to be related to the protocol and on-study deaths, including death of a research subject unless the death is expected (e.g. due to disease progression) to be reported to the DSMC within 24 hours for medical monitor ad hoc review between meetings to determine if immediate action is required. Reports may be emailed to the DSMC Admin at GroupSOCCICCTODSMCAdmin@cshs.org.

6.4.3 Reporting to the Institutional Review Board (IRB)

The CSMC IRB requires that investigators report all adverse events that may represent an unanticipated problem involving risks to subjects or others as defined below.

All adverse events (those involving subjects who were enrolled at CSMC) which are both unexpected and probably related to the research must be reported to the IRB.

All reportable events should be submitted in CS-IRB to the Office of Research Compliance and Quality Improvement as ***soon as possible, but no more than 10 days from the investigator's awareness of the event***.

The report must contain at least:

- Identification of the PI, study coordinator (if applicable), contact information, study title, and IRB number.

- A detailed summary of the problem, including all relevant details and the PI's assessment of the events leading up to the problem, to assist the IRB in its evaluation.
- A description of any action taken to address or remedy the problem, including a description of the resolution, if any, or current status.
- An assessment as to whether any changes are required in the conduct of the research to resolve the problem or prevent further problems.

6.4.4 Reporting to the Food and Drug Administration (FDA)

The investigator or his designee must submit documentation of adverse reactions according to the following reporting criteria:

- Reporting any unexpected fatal or life-threatening suspected adverse reactions no later than **7 calendar days** after initial receipt of the information

- Reporting any (1) serious, unexpected suspected adverse reactions, (2) findings from other clinical, animal, or in-vitro studies that suggest significant human risk, and (3) a clinically important increase in the rate of a serious suspected adverse reaction no later than **15 calendar days** after determining that the information qualifies for reporting.

6.4.5 Expedited Reporting to Merck

All Adverse events will be documented according to GCP and graded according to CTCAE. **SAE reports and any other relevant safety information are to be forwarded to the Merck Global Safety facsimile number: +1-215-661-6229.**

Alternatively, reports may be called into the Merck National Service Center at 1-800-444-2080, or sent via secure email to Whitney.Sarchiapone@merck.com.

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.

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

7.0 DRUG INFORMATION

7.1 Pembrolizumab

See current version of the Investigator's Brochure.
Study drug will be provided by Merck.

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. Clinical Supplies will be provided by Merck as summarized below:

Product Descriptions

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

7.1.1 Packaging and Labeling Information

Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

7.1.2 Clinical Supplies Disclosure

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

7.1.3 Storage and Handling Requirements

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

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

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

7.1.4 Returns and Reconciliation

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

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

7.2 Olaparib

See current version of the package insert. Olaparib supply will be provided by Merck. Commercial supply will be used.

Olaparib will be provided as marketed packs of Lynparza (100 mg and 150 mg tablets in bottles of 120 tablets). Approved dosage is 300 mg (two 150 mg tablets) twice daily for a total daily dose of 600 mg daily. To manage adverse reactions, dose reduce to 250 mg (one 150 mg tablet and one 100 mg tablet) twice daily for a total daily dose of 500 mg. If further dose reduction is required, dose reduce to 200 mg (two 100 mg tablets) twice daily for a total daily dose of 400 mg.

8.0 CORRELATIVES/RESEARCH STUDIES

The main objective of the translational research component of the IIT is to obtain biomarker measurements of PD-1 and PD-L1 expressions. Archival tumor samples will be sent to Qualtek Molecular Laboratories for analysis. See Sample Handling Manual.

9.0 STATISTICAL CONSIDERATIONS

Therapy administered until documented/confirmed progression by RECIST 1.1 criteria. This trial is a pilot study to assess the objective response rate with immunotherapy and PARP inhibition.

There are no preliminary statistical assumptions. First response assessments at 9 weeks; time interval for trial assessment is typical for time interval for assessment of response to standard of care therapy. Investigational therapy will not preclude subsequent standard of care therapy or subsequent investigational therapy.

9.1 Study Design/Study Endpoints

This study is a pilot study intended to determine ORR to single agent pembrolizumab in addition to standard of care olaparib treatment in study population.

9.2 Sample Size and Early Stopping

Clinical benefit is defined as complete response, partial response, or stable disease (if stable disease, lasting for at least four months). A proportion of patients with clinical benefit less than 15% will be of no interest. The new treatment would be of interest if the proportion of patients with clinical benefit is at least 41%. Simon's two-stage design (Simon, 1989) will be used. The null hypothesis: p<= 0.15 is against the alternative hypothesis p>= 0.41. In the first stage, 10 patients will be accrued. If there are 2 or fewer subjects with clinical benefit among these 10 patients, the study will be terminated. The probability of early stopping under the null is 0.82, and under the alternative is 0.16. Otherwise, 10 additional patients will be accrued for a total of 20. The null hypothesis will be rejected if 6 or more responses are observed in 20 patients. This design yields a 1-sided type I error rate of 5% and power of 80%.

The early stopping rule is based on responses in the first 10 patients, rather than dose limiting toxicity, as the study drug is FDA-approved at the current dose used in this trial, has a known and predictable rate of toxicity at the present dose, has been used in prior cohorts of breast cancer patients at the current dose, and there is no biological basis on which to expect excessive or unusual toxicity in the study cohort.

9.3 Data Analysis Plans

Data will be analyzed after enrollment and tumor assessments of the first 10 subjects to determine whether early stopping point has been met.

Analysis of Endpoints

9.3.1 Exploratory Data Analysis: Exploratory analyses will be performed to elucidate the relationships among variables. Graphical data analysis will be applied to examine the distribution of the data and to reveal the association among covariates and outcome variables. Statistical graphics provide effective data summaries and can be very useful for error checking and outlier identification. Standard distribution plots such as histograms and box-plots will be applied. A scatter plot matrix will be used to explore the association among multiple variables. The main purpose of the exploratory data analysis is to "let the data speak". These analyses not only provide an assumption free, graphical, presentation of the data, but can also be used to help select appropriate statistical models to use during data analysis.

9.3.2 Analysis of Survival Data: We will estimate the survival distributions for time-to-event outcomes using the method of Kaplan and Meier and compare these distributions among groups using the logrank test. Multivariable proportional hazards regression models will be used to assess which biomarkers are predictive of patient outcomes in the presence of covariates. The proportional hazards assumption will be evaluated graphically and analytically, and regression diagnostics (e.g., martingale and Shoenfeld residuals) will be examined to ensure that the models are appropriate. Violations of the proportional hazards assumption will be addressed by use of time-dependent covariates or extended Cox models. The possibility of collinearity will be reduced through the careful initial assessment of correlations among all study covariates.

9.3.3 Analysis of Categorical Response Variables: We will test for differences among groups using Pearson's chi-square statistic, or Fisher's exact test. In those situations where we must stratify on a characteristic of the population under study, we may employ the Cochran-Mantel-Haenszel test. In those situations in which we are interested in modeling the relationship between a binary response variable and single or multiple covariates, we will use logistic regression. Logistic regression diagnostics will be employed to ensure that the logistic model is appropriate. Similarly, the possibility of collinearity will be reduced through the careful initial assessment of correlations among all study covariates.

9.3.4 Analysis of Continuous Response Variables: For the analysis of continuous response variables, we will use analysis of variance (ANOVA), analysis of covariance (ANCOVA), and mixed models. We will test the data to ensure that the underlying assumptions (i.e., normality, homoscedasticity) of the ANOVA model are met. If these assumptions are not met, then we will attempt to transform the data such that the transformed data meet these assumptions. Standard transformations of the response variable such as the log, square root and Box-Cox transformations will be examined. If data transformation is inadequate to meet the analysis assumptions, then rank transformation of the data will be performed and one-way ANOVA on the rank transformed response variables will be analyzed and reported. In those situations where covariates could potentially have an effect on the response variable in an ANOVA context, we will use ANCOVA to adjust treatment effects. The underlying assumptions of the ANCOVA model will be tested (such as homogeneity of slopes across groups). Standard regression criteria will be used to assess appropriateness of including particular covariates. In situations where more than one covariate is being included in the model, the possibility of collinearity will be reduced through the careful initial assessment of correlations among all study covariates.

9.3.5 Analysis of Biomarker Data: Associations between biomarkers will be assessed using Cohen's Kappa with appropriate 95 percent confidence intervals reported. Kappas of .75 or greater are considered excellent, whereas Kappas between .4 and .75 denote good agreement.

10.0 STUDY MANAGEMENT

10.1 Conflict of Interest

Any reportable conflict of interest will be disclosed to the local IRB and will be outlined in the Informed Consent Form.

10.2 Institutional Review Board (IRB) Approval and Consent

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations.

Any documents that the IRB may need to fulfill its responsibilities (such as protocol, protocol amendments, Investigator's Brochure, consent forms, information concerning patient recruitment, payment or compensation procedures, or other pertinent information) will be submitted to the IRB. The IRB's written approval of the study protocol and the informed consent form will be in the possession of the Investigator before the study is initiated and prior to the shipment of study supplies to participating sites, if applicable. This approval must refer to the study by exact protocol title and number and should identify the documents reviewed and the date of review.

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

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

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

10.3 Registration Procedures

All patients will be tracked following written informed consent. Those patients who are consented to participate in the clinical trial but do not meet one or more criteria required for participation during the screening phase will be listed as screen failures on the master list of consented subjects. Eligible subjects, as determined by screening procedures and verified by a treating investigator, will be registered on study at Cedars Sinai Medical Center by the Study Coordinator.

Issues that would cause treatment delays after registration should be discussed with the Principal Investigator (PI). If a patient does not receive protocol therapy following registration, the patient's registration on the study may be canceled. The Study Coordinator should be notified of cancellations as soon as possible.

Assignment of Subject ID: The study team will track all subjects who sign consent using OnCore. Subjects found to be ineligible will be recorded as screen failures. Subjects

found to be eligible will be registered using a three-digit numeric ID that follows the standard SOCCI format (001, 002, etc.).

A) Eligibility Verification

Prior to registration, all subjects must undergo eligibility verification by the SOCCI Cancer Clinical Trials Office (CCTO) Quality Management Core (QMC). The following documents will be organized into an eligibility packet, scanned as a pdf, and emailed to GroupSOCCICROQMC@cshs.org for review:

- QMC approved Eligibility Checklist signed by investigator and 2 members of the study team (or equivalent)
- Source documents substantiating eligibility that cannot be located in the subject's CS Link medical record
- Signed consent form with Subject's Bill of Rights, HIPAA authorization form, consent progress note, and any optional consent forms, as applicable, if not available in CS Link

B) Registration

After eligibility is verified, each site will assign the subject a study number and site staff will then register the patient in OnCore®.

Registration is completed as follows:

- Assign a patient study number
- Enter the patient in OnCore
- Notify the investigational pharmacy and treating physicians that a subject has gone on study and anticipated treatment start date

  Oversight by the principal investigator is required throughout the entire registration process

10.4 Data Management and Quality Control and Reporting

REDCap is the Cedars-Sinai Cancer institutional choice for the electronic data capture of case report forms for SOCCI Investigator Initiated Trials. REDCap, a HIPAA-compliant database, will be used for electronic case report forms in accordance with institutional requirements, as appropriate for the project. The Study Staff will be responsible for data processing, in accordance with procedural documentation. Database lock will occur once quality assurance procedures have been completed. See also Section 10.5.2, Monitoring.

All procedures for the handling and analysis of data will be conducted using good computing practices meeting FDA guidelines for the handling and analysis of data for clinical trials.

10.5 Data and Safety Monitoring

10.5.1 Safety Oversight

Adherence to the protocol, Good Clinical Practices (GCP), and institutional policy will be monitored by the PI during the course of the study through routine Disease Research Group (DRG) meetings (or equivalent). The PI will maintain continuous safety monitoring for the duration of the study by reviewing subject/study data. It is the responsibility of the

principal investigator to adhere to the Data Safety Monitoring Plan throughout the life of the study.

In addition, safety oversight and efficacy data will be reviewed by the SOCC Data and Safety Monitoring Committee (DSMC). The DSMC will review this trial commensurate with the assigned risk class as categorized by the PRMC. The DSMC membership and responsibilities are governed by the committee charter. The DSMC findings and recommendations will be reported in writing to the Principal Investigator as a summary letter which will be forwarded by the Principal Investigator or designee to the CS-IRB. The DSMC outcome letters will be furnished to the FDA, as applicable. Refer to the DSMC Charter for details of the DSMC review.

10.5.2 Monitoring

The SOCC Cancer Clinical Trials Office (CCTO) Quality Management Core (QMC) will conduct internal monitoring visits and audits to ensure that the rights and well-being of trial 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 International Conference on Harmonisation Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s).

Refer to the DSMP for details pertaining to the type, frequency, and extent of monitoring that will be performed.

10.6 Record Retention

Study documentation includes all Case Report Forms, data correction forms or queries, source documents, monitoring/auditing logs/letters, records of study drug receipt, dispensation, destruction and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms). Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study. Government agency regulations and directives require that the study investigator must retain all study documentation pertaining to the conduct of a clinical trial. Study documents should be kept on file in accordance with all applicable federal guidelines and local guidelines.

Investigators must make study data accessible to the monitor, other authorized representatives of the Sponsor (or designee), IRB, and Regulatory Agency (e.g., FDA) inspectors upon request.

10.7 Adherence to the Protocol

It is the responsibility of the Investigator-sponsor to ensure that patient recruitment and enrollment, treatment, follow-up for toxicities and response, and documentation and reporting at SOCCI are all performed as specified in the protocol. For multi-site studies, the site Principal Investigator at each participating site will assume the responsibilities for the day-to-day monitoring of the trial, including but not limited to review of eligibility of new subjects, proper documentation informed consent, administration of treatment per protocol, thorough documentation and capturing of research notes in the subject's charts, and timely completion of required case report forms. Except for an emergency situation in which proper care for the protection, safety, and well-being of the study patient requires alternative treatment, or a protocol exception request approved by the SOCCI Medical Director and IRB of record, the study shall be conducted exactly as described in the approved protocol.

10.7.1 Emergency Modifications

Investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB approval.

For any such emergency modification implemented, the IRB must be notified as soon as possible, but no more than 72 hours from the investigator's awareness of the event.

10.7.2 Protocol Exceptions and Eligibility Waivers

A protocol exception is an anticipated or planned deviation from the IRB-approved research protocol, as described in the IRB Policy, *Reporting Possible Unanticipated Problems Involving Risks to Subject or Others (UPIRSO) Policy: Institutional Review Board/Research Compliance and Quality Improvement.* A protocol exception most often involves a single subject and is not a permanent revision to the research protocol. Protocol exceptions that extend beyond a single subject should result in a protocol amendment to avoid serial violations.

Planned exceptions to the protocol that are more than logistical in nature and/or affect timing of study drug administration, or the investigator assesses the event may impact subject safety and/or study integrity, may not be implemented without prior approval from the SOCCI CCTO Medical Director and the IRB. The PI or her/his designee is responsible for submitting a protocol exception and its supporting documents to the SOCCI CCTO Medical Director for review and further instructions on IRB reporting.

Study team should refer to the IRB *Reporting Possible Unanticipated Problems Involving Risks to Subject or Others (UPIRSO) Policy: Institutional Review Board/Research Compliance and Quality Improvement* guidelines to determine which deviations and exception requests meet reporting guidelines. Once approved by the medical director, the deviation or exception request must be submitted to the IRB for review and approval prior to implementation.

Special considerations for Eligibility Waivers (EW)
Subjects who do not meet the eligibility requirements should not be enrolled. Eligibility waivers are not permitted.

Exception Request Submission Process
The PI and/or treating physician should provide a written request for a protocol exception including case history and justification for prospective deviation from the study design to the SOCCI CCTO Medical Director. The "IIT Exception Requests (ER) Form" must be completed then submitted, along with any applicable supporting documents, must be emailed to QMC (GroupSOCCICROQMC@cshs.org) to request a protocol exception from the CCTO Medical Director. This is only a requirement for studies with a DSM classification of moderate or high. An assessment from the CCTO Medical Director or designee must be done prior to submission to the IRB for review.

10.7.3 Other Protocol Deviations/Violations

Logistical deviations from the protocol (e.g., minor changes to the study schedule for an individual subject) do not require prior IRB approval unless the deviation has the potential to affect the subject's safety or study integrity. Such planned deviations that do meet this definition and do not affect the subject's safety or study integrity should be noted in the subject's research record or deviation log

as described in the SOCCI CCTO's Standard Operating Procedure 12: Deviation and Noncompliance Reporting.

Unintentional deviations from the protocol that might affect subject safety or study integrity should be reported to the IRB within 10 days from when the investigator becomes aware that such a deviation has occurred, as outlined in the SOCCI CCTO's Standard Operating Procedure 12: *Deviation and Noncompliance Reporting*. In this case, a Protocol Deviation report must be submitted in CS-IRB, per CSMC IRB policy, *Reporting Possible Unanticipated Problems Involving Risks to Subject or Others (UPIRSO) Policy: Institutional Review Board/Research Compliance and Quality Improvement.*
All submissions should include a description of the plan to avoid similar deviations or exceptions in the future.

10.8 Amendments to the Protocol

Should amendments to the protocol be required, the amendments will be originated and documented by the Principal Investigator. It should also be noted that when an amendment to the protocol substantially alters the study design or the potential risk to the patient, a revised consent form might be required.

The written amendment, and if required the amended consent form, must be sent to the IRB for approval prior to implementation. Repeat exceptions or deviations to the protocol may suggest a protocol amendment is needed.

10.9 Obligations of Investigators

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

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

10.10 Publications

The preparation and submittal for publication of manuscripts containing the study results shall be in accordance with a process determined by mutual written agreement among the sponsor-investigator and participating institutions. The publication or presentation of any study results shall comply with all applicable privacy laws, including, but not limited to, the Health Insurance Portability and Accountability Act of 1996.

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12.0 Appendix: Acceptable Birth Control Methods

Olaparib is regarded as a compound with medium/high foetal risk.

Women of childbearing potential and their partners, who are sexually active, must agree to the use of TWO highly effective forms of contraception in combination [as listed below]. This should be started from the signing of the informed consent and continue throughout the period of taking study treatment and for at least 1 month after last dose of study drug(s), or they must totally/truly abstain from any form of sexual intercourse (see below).

Male patients must use a condom during treatment and for 3 months after the last dose of olaparib when having sexual intercourse with a pregnant woman or with a woman of childbearing potential. Female partners of male patients should also use a highly effective form of contraception if they are of childbearing potential (as listed below). Male patients should not donate sperm throughout the period of taking olaparib and for 3 months following the last dose of olaparib.

Acceptable Non-hormonal birth control methods include:

Total/True abstinence: When the patient refrains from any form of sexual intercourse and this is in line with their usual and/or preferred lifestyle; this must continue for the total duration of the trial and for at least 1 month after the last dose of study drug <<for 3 months after last dose *for male patients*>>. [Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods, or declaration of abstinence solely for the duration of a trial) and withdrawal are not acceptable methods of contraception]

Vasectomised sexual partner PLUS male condom. With participant assurance that partner received post-vasectomy confirmation of azoospermia.

Tubal occlusion PLUS male condom

IUD PLUS male condom. Provided coils are copper-banded

Acceptable hormonal methods:

Normal and low dose combined oral pills PLUS male condom

Cerazette (desogestrel) PLUS male condom. Cerazette is currently the only highly efficacious progesterone based pill.

Hormonal shot or injection (eg., Depo-Provera) PLUS male condom

Etonogestrel implants (e.g., Implanon, Norplant) PLUS male condom

Norelgestromin / EE transdermal system PLUS male condom

Intrauterine system [IUS] device (eg., levonorgestrel releasing IUS -Mirena®) PLUS male condom

Intravaginal device (e.g., EE and etonogestrel) PLUS male condom

13.0 Summary of Changes

Protocol Amendment 1 (Protocol Version 2 dated 07 NOV 2017)

- Updates to Section 5.13: Time and Events Table
  - Addition of Thyroid lab panel (Free T3, Free T4, TSH) time points at C2D1 and C6D1.
  - Removal of Pembro Administration timepoint at C1D8.
  - Addition of +/- 3 day window to treatment phase procedures.
  - Addition of Hematology and Chemistry time points at C1D1, C1D8, C1D15.

Protocol Amendment 2 (Protocol Version 3 dated 21 DEC 2017)

- Addition of Co-Investigators: Alain Mita, MD; Reva Basho MD; Bobbie Rimel; MD
- Section 4.1: Addition of Table 3: Dose Modification and Toxicity Management Guidelines for Immune-related AEs Associated with Pembrolizumab
- Section 4.3: Clarification to allow for palliative radiation
- Section 5.12: Modification to Time and Events Table
  - Clarification that Pembro administration will occur Q3W D1 of each cycle. Addition of check box at C2D1.

Protocol Amendment 3 (Protocol Version 4 dated 12 MAR 2020)

- Cover page:
  - Updated study title.
  - Removal of co-investigator Dr. Julie Dunhill.
- Study Schema: Updated to add treatment with olaparib.
- Study Summary:
  - Updated to add treatment with olaparib.
  - Increased accrual duration to 36 months.
  - Increased duration of trial to 42 months.
- Section 1.0 Background and Rationale: Updated to reflect treatment with olaparib, inclusion of subjects with or without prior PARP-inhibitor exposure, and rationale for allowing subjects with ER+/PR+ disease to continue endocrine therapy. Updated with most current pembrolizumab data.
- Section 2.1 Primary Objective: Revised to reflect treatment with olaparib.
- Section 2.2 Secondary Objectives: Revised for consistency with protocol inclusion criteria.
- Section 3.1 Inclusion Criteria:
  - 3.1.8 Revised table of adequate organ fucntion per updated Merck template.
- Section 3.2 Exclusion Criteria:
  - 3.2.4 Clarification to allow inclusion of ER+/PR+ subjects receiving endocrine therapy; subjects with HER2+ disease will be required to discontinue Herceptin (trastuzumab).
  - 3.2.5.1 Clarification to allow inclusion of patients with or without prior PARP-inhibitor exposure.
  - 3.2.12. Added examples of live vaccines per Merck template.
- Section 4.1 Treatment Dosage and Administration and Section 4.2.2 Toxicities and Dosing Delays: Addition of olaparib treatment per standard of care and subject completion of compliance diary.
- Section 4.2.1. Pembrolizumab: Updated toxicity management guidelines per Merck template.
- Section 4.2.2. Olaparib: New section referring to olaparib package insert.

- Section 4.3 Concomitant Medications: Clarification that subjects with ER+/PR+ disease may continue endocrine therapy; subjects with HER2+ disease will be required to discontinue Herceptin (trastuzumab).
- Section 4.4. Supportive Care Guidelines: Edited to follow updated Merck template.
- Section 4.5 Duration of Therapy: Addition of olaparib
- Section 4.6 Duration of Follow-up: Removal of re-treatment with pembrolizumab.
- Section 5.0 Study Procedures: Addition of EKG at baseline.
- Section 5.7 Laboratory Safety Evaluations: Addition of coagulation parameters
- Section 5.14 Time and Events Table:
    - Addition of EKG at baseline
    - Addition of CBC and CMP at C2 D8.
    - Addition of coagulation parameters
    - Addition of olaparib daily dosing and compliance diary completion.
    - Addition of footnotes 7-9 for consistency with Merck safety language and addition of olaparib.
    - Minor clarification to footnote 5; addition of footnote 10 for clarification.
- Section 6.1.2 Adverse Events: Addition of AE collection for events determined to be unexpected and at least possibly related to olaparib.
- Section 6.4 Data Collection Procedures for Adverse Events: Clarification that abnormal laboratory findings of no clinical significance are not considered reportable AEs.
- Section 6.5.2 Expedited Reporting: Addition of boilerplate language for reporting to DSMC.
- Section 6.5.3 Reporting to the Institutional Review Board: Updated to reflect revised IRB reporting policy.
- Section 7.0 Drug Information: Addition of olaparib; revisions to follow updated Merck template.
- Section 10 Study Management: Updated institutional boilerplate language.
- Addition of Olaparib Dosing Diary (separate document).

Protocol Amendment 4 (Protocol Version 4.1 dated 15 SEP 2020)

- Cover page: Removal of co-investigator Dr. Sarna.
- Section 5.14 Time and Events Table, footnote 8: Clarification that Olaparib dosing must begin within 3 days of pembrolizumab C1D1.
- Section 6.4 Steps to Determine if an Adverse Event Requires Expedited Reporting, Section 6.6.1 Expedited Reporting to PI: Clarification that SAEs and ECIs should be reported for 90 days after last pembrolizumab dose or until new anticancer treatment is initiated, but for a minimum of 30 days, whichever occurs first.
- Section 6.4 Steps to Determine if an Adverse Event Requires Expedited Reporting: Clarification of sources of current known adverse events.
- Section 6.5 Data Collection Procedures for Adverse Events: Clarification of adverse event reporting timeframe.

Protocol Version 5 dated 19APR2021

- Inclusion criterion 3.1.6: Inclusion of BRCA somatic mutations.
- Exclusion criterion 3.2.2: Minor formatting change for clarification.
- Exclusion criterion 3.2.12 and Section 4.3.2 Prohibited Concomitant Medications have been revised regarding vaccine administration per Merck's revised pembrolizumab protocol template.
- Section 4.2.1 Pembrolizumab and Table 3 have been updated per Merck's revised pembrolizumab protocol template.
- Section 4.5 Duration of Therapy: The maximum duration of study treatment will be 35 administrations of pembrolizumab (approximately 2 years).
- Addition of Section 4.8 Subject Replacement and Evaluability Guidelines
- Section 5.15 Time and Events table:

  - Timing of tumor marker measurements will be as per standard of care, at the investigator's discretion
  - Footnote 3: The maximum duration of study treatment will be 35 administrations of pembrolizumab (approximately 2 years).
  - Addition of footnote 11: The archival tumor tissue for correlative studies may be sent to QualTek any time after eligibility verification.
- Section 6.1.2 Events of Clinical Interest: Incorporation of pembrolizumab template language for overdose.
- Section 6.4.5 Expedited Reporting to Merck: Addition of phone and email reporting options.
- Section 9.2 Sample Size and Early Stopping: Clarification of the definition of favorable response/clinical benefit relevant to the early stopping rule.
- Section 9.3 Data Analysis Plans: Deletion of inconsistent definition of early stopping rule.

Protocol Version 6 dated 16JUL2021

- Cover page: Removal of co-investigator Rimel; addition of co-investigator El-Masry
- Throughout protocol:
  - Addition of HDR-defect cohort
  - Addition of Tempus HRD testing at screening for subjects who do not qualify based on BRCA status
  - Change in olaparib from standard of care drug to research drug, due to addition of HDR-defect cohort. Incorporation of olaparib protocol template language in the following sections:
    - Sections 3.1-3.2: Inclusion/exclusion criteria
    - Section 4.1.1: Meals and dietary restrictions
    - Section 4.3 Concomitant Medications/Treatments
    - Section 4.2.2 Olaparib Dose Reductions
    - Section 4.2.3 Olaparib Management of Adverse Events
    - Section 6.1.2.1 Olaparib Overdose
    - Section 12: Appendix: Acceptable Birth Control Methods
- Study Schema, Study Summary, and Section 1.4 Rationale: Correction to include subjects with somatic BRCA mutations.
- Section 4.5 Duration of Therapy: Addition of parameters for subjects to remain on treatment following initial disease progression by RECIST 1.1. until confirmation of progression 4-8 weeks later.
- Section 5 Study Procedures: Screening window extended from four weeks to six weeks prior to C1D1.
- Section 5.15 Time and Events table:
  - Screening window extended from four weeks to six weeks prior to C1D1.
  - Addition of Tempus HRD testing and footnote 12
  - Addition of +/- 7 day window for end-of-treatment visit.
- Addition of Section 7.2: Olaparib drug information.

Protocol version 7 dated 03AUG2021

- Removed Dr. McArthur as an Investigator

- **Exploratory Objectives, Section 2.3.1:** Removed exploratory objective related to (ir) RECIST

  ~~2.3.1 Exploratory: ORR, PFS, CBR and DOR based on immune-related (ir)RECIST as assessed by local investigator/local radiology.~~

- **Correlative Objectives, Section 2.3.1:** Renumbered Correlative Study section

  2.3.1~~2~~ Correlative Studies

- **Study Summary, page 3 & Inclusion Criteria, Section 3.1.3:** Revised prior line therapy inclusion criteria to allow 1st line therapy for patients who have progressed within 12 months following neoadjuvant or adjuvant treatment.

  3.1.3 Advanced BRCA-mutated and/or HDR-defect breast cancer progressing on or after prior therapy for metastatic disease or locally advanced disease; Prior therapy is defined as follows: for triple negative breast cancer – progressing after at least 1 line of any prior chemotherapy; for HER2 positive disease must have progressed after at least two HER2 directed therapies in the metastatic setting including ado-trastuzumab emtansine (T-DM1); for hormone receptor positive disease (ER, PR, or both) must have progressed after palbociclib plus hormonal therapy . Patients with progression within 12 months from previous neoadjuvant or adjuvant treatment could be enrolled in the study as 1st line therapy in metastatic setting.

- **Exclusion Criteria, Section 3.2.5:** Revised exclusion criteria to allow for patients who were on previous immunotherapy treatment.

  ~~3.2.5 Has received prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways).~~ Has participated in another MK03475 trial.

- **Events of Clinical Interest, Section 6.1.2 & Expedited Reporting to Merck, Section, 5.4.5:** Update the fax number for reporting adverse events to Merck, per the recent contract amendment.

FAX 215 ~~993~~661 ~~1220~~6229

Protocol v8 dated 11MAR2022

- **Study Summary and Section 3.1, Inclusion Criteria:**

  - Expand recruitment to allow patients who have progressed on any CDK4/CDK6 inhibitor.

    3.1.3 Advanced BRCA-mutated and/or HDR-defect breast cancer progressing on or after prior therapy for metastatic disease or locally advanced disease; Prior therapy is defined as follows: for triple negative breast cancer – progressing after at least 1 line of any prior chemotherapy; for HER2 positive disease must have progressed after at least two HER2 directed therapies in the metastatic setting including ado-trastuzumab emtansine (T-DM1); for hormone receptor positive disease (ER, PR, or both) must have progressed after ~~palbociclib~~ **a CDK4/CDK6 inhibitor** plus hormonal therapy.

- **Section 4.5, Duration of Therapy:**

  - Clarify the methods for confirming disease progression.

    In patients with initial disease progression substantiated by radiographic imaging per RECIST 1.1, study treatment may continue until repeat imaging is conducted, at least 4 weeks and no later than 8 weeks later, under the following conditions:

    - No worsening of ECOG Performance Status
    - No clinically relevant increases in disease-related symptoms thought to be associated with disease progression
    - No requirement for intensified management of disease-related symptoms exists, including increased analgesia, radiotherapy, or other palliative care.

Disease progression can also be confirmed histologically, cytologically, or surgically, or by physical examination or other clinical signs, per PI discretion.

Protocol v9 dated 05DEC2023

- Removed Dr. Basho as Co-I.
- Biostatistician updated to Marie Lauzon, MS
- Section 5.15 Time and Events Table: Removal of erroneous footnote 6.
- Section 10: Updated throughout to current boilerplate template language.