UCSF Helen Diller Family Comprehensive Cancer Center

Phase 2 open label study of pembrolizumab in patients with metastatic castration resistant prostate cancer (mCRPC) with or without DNA damage repair defects

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PROTOCOL SIGNATURE PAGE

Protocol No.: 16557 **Version Date:** 11-25-2019

1. I agree to follow this protocol version as approved by the UCSF Protocol Review Committee (PRC), Institutional Review Board (IRB), and Data Safety Monitoring Committee (DSMC).
2. I will conduct the study in accordance with applicable IRB requirements, Federal regulations, and state and local laws to maintain the protection of the rights and welfare of study participants.
3. I certify that I, and the study staff, have received the requisite training to conduct this research protocol.
4. I have read and understand the information in the Investigators' Brochure (or Manufacturer's Brochure) regarding the risks and potential benefits. I agree to conduct the protocol in accordance with Good Clinical Practices (ICH-GCP), the applicable ethical principles, the Statement of Investigator (Form FDA 1572), and with local regulatory requirements. In accordance with the FDA Modernization Act, I will ensure the registration of the trial on the www.clinicaltrials.gov website.
5. I agree to maintain adequate and accurate records in accordance with IRB policies, Federal, state and local laws and regulations.

Principal Investigator

_____
Printed Name

_____ _____
Signature Date

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1.0 TRIAL SUMMARY

Abbreviated Title	Phase 2 pembrolizumab in mCRPC with or without DNA damage repair defects
Trial Phase	2
Clinical Indication	Metastatic castration resistant prostate cancer (mCRPC) after prior abiraterone and/or enzalutamide
Trial Type	Phase 2, non-randomized, comparative study
Type of control	- No treatment control. - Negative DNA damage repair defect signature as biomarker control.
Route of administration	Intravenous
Trial Blinding	No blinding.
Treatment Groups	- Group 1: DNA damage repair proficient group - Group 2: DNA damage repair defective group Patients with previously identified MSI-high tumor by PCR or IHC, or homozygous deletion or deleterious germline or somatic mutation(s) in DNA damage repair gene(s) (such as *BRCA1*, *BRCA2* and *ATM*) identified in a CLIA-certified laboratory are allowed in Group 2.
Number of trial subjects	50 subjects total (25 subjects in each study group)
Estimated enrollment period	24 months
Estimated duration of trial	36 months
Duration of Participation	- Until progression of disease or unacceptable toxicity. - Subjects who progress and choose to receive taxane-based chemotherapy (docetaxel or cabazitaxel with or without a platinum agent, e.g. carboplatin) for 2-8 cycles have the option to repeat pembrolizumab until progression of disease or unacceptable toxicity, assuming response to chemotherapy.
Estimated average length of treatment per patient	4 months (shorter for DNA damage repair proficient group; longer for DNA damage repair defective group)

2.0 TRIAL DESIGN

2.1 Trial Design

This is a phase 2 open label study of pembrolizumab in patients with metastatic castrate resistant prostate cancer (mCRPC) with or without DNA damage repair defects. All patients must have received prior secondary hormonal therapy.

At the time of screening, subjects will undergo mandatory biopsy of primary or metastatic tissue to determine DNA repair gene mutation and/or MSI signature status. Both tests are performed in a CLIA certified laboratory. MSI testing will be performed by the PCR based Promega assay at UCSF with a turn-around time of 1-2 weeks.

Subjects will be assigned to one of two treatment groups:

- Group 1 (DNA damage repair proficient group): Twenty-five subjects with MMR intact by having no DNA repair gene mutations by panel sequencing

- Group 2 (DNA damage repair deficient group): Twenty-five subjects with MSI-high and/or DNA repair gene mutations.

    - Patients with previously identified MSI-high tumor by PCR or IHC, or homozygous deletion or deleterious germline or somatic mutation(s) in DNA damage repair gene(s) (such as *BRCA1*, *BRCA2*, and *ATM)* identified in a CLIA-certified laboratory are allowed in Group 2.

All subjects will receive pembrolizumab 200mg IV every 3 weeks until disease progression or unacceptable toxicity. The primary endpoint of the study is radiographic progression-free survival (rPFS).

Because the DNA damage repair defective signature is anticipated to be present in only ~20% of screened subjects, Group 1 is anticipated to complete enrollment before Group 2. To facilitate initial accrual, we will enroll the initial patients onto the clinical trial and begin treatment without having the full results of the DNA repair status available so long as Group 1 has slots available (i.e. at least the initial 25 patients). Once Group 1 is fully enrolled (and DNA damage repair status verified for those subjects), DNA damage repair defective status must be confirmed before subjects can enroll to the remaining slots in Group 2. Approximately 125 subjects are anticipated to be screened to complete enrollment in both groups.

Subjects who progress on pembrolizumab in either study group will have the option of undergoing biopsy of a metastatic site. At time of progression, all subjects will also have the option of receiving taxane-based chemotherapy followed by repeat pembrolizumab for those who have a clinical response to chemotherapy. Subjects who reinitiate pembrolizumab following chemotherapy will have the option of undergoing an additional biopsy of the metastatic site. Chemotherapy regimen will be at the discretion of the treating physician, and may consist of docetaxel or cabazitaxel with or without a platinum agent (e.g. carboplatin). A minimum of 2 cycles and a maximum of 8 cycles of chemotherapy will be given. Clinical response to chemotherapy is defined as PSA decrease by >50% or objective response by RECIST v1.1.

Inclusion of patients onto Group 1 is important for several reasons. First, while the study aims to elucidate whether DNA damage repair defects could be a predictive biomarker to PD-1 blockade, this is the hypothesis that is being tested and it is unknown whether this is the case. Assessing clinical response rates in the two study groups will address this question. Second, a key component of the protocol is to assess whether chemotherapy "rescues" non-responders to derive benefit from anti-PD-1 blockade, regardless of whether the tumor harbors DNA damage repair defects. Lastly, the clinical response to pembrolizumab in patients with mCRPC may be more than previously anticipated. Preliminary data from KEYNOTE-028 showed that 3 of 23 mCRPC patients achieved partial response (Hansen A et al. 2016). A phase 2 study of pembrolizumab in enzalutamide-resistant mCRPC patients showed that 3 of 10 patients achieved partial response, one of whom harbored MMR deficiency (Graff JN et al. 2016).

3.0 OBJECTIVES & HYPOTHESES

3.1 Primary Objective & Hypothesis

(1) **Objective:** To compare the radiographic progression-free survival (rPFS) in mCRPC subjects with proficient DNA damage repair (Group 1) and defective DNA damage repair (Group 2), using PCWG3 criteria.

Hypothesis: mCRPC patients whose tumors have defective DNA damage repair have improved response to pembrolizumab compared to patients whose tumors have proficient DNA damage repair.

3.2 Secondary Objectives & Hypotheses

(1) **Objective**: To compare rate of immune-related progression-free survival (irPFS) and PFS at 20 weeks and 28 weeks in both study groups, using irRC and RECIST v.1.1.

Hypothesis: Subjects whose tumors have defective DNA damage repair have longer irPFS and PFS than those whose tumors have proficient DNA damage repair.

(2) **Objective:** To compare the proportion of subjects achieving any PSA response and PSA decline ≥50% from baseline in both study groups.

Hypothesis: A higher proportion of subjects whose tumors have defective DNA repair will achieve PSA response than those whose tumors have proficient DNA repair.

(3) **Objective:** To assess the safety of pembrolizumab in both study groups by CTCAE v4.0.

Hypothesis: Pembrolizumab is well tolerated in subjects with mCRPC in both study groups.

(4) **Objective:** To compare time to progression after taxane-based chemotherapy in subjects who initially progress on pembrolizumab, undergo taxane-based chemotherapy, followed by repeat pembrolizumab in both study groups.

Hypothesis: Taxane-based chemotherapy increases the visibility of tumor antigens and recaptures response to pembrolizumab in some subjects in both study groups.

3.3 Exploratory Objectives

(1) To assess immune infiltration and PD-L1 staining in mandatory baseline tumor tissue biopsy and optional progression biopsy tissues, and correlate immune infiltration and PD-L1 positivity to DNA damage repair signature and clinical outcomes.

(2) To assess baseline circulating T cell receptor (TCR) repertories and changes in TCR repertories with treatment, and correlate baseline and turnover of repertories to DNA damage repair signature and clinical outcomes.

(3) To assess tumor mutational burden (number of somatic mutations) in a subset of subjects in both study groups, and correlate mutational burden with DNA damage repair signature and clinical outcomes.

(4) To assess changes in circulating immune cells with treatment, and correlate changes with DNA damage repair signature and clinical outcomes.

(5) To assess the concordance rate of MSI status and FA/BRCA signature between paired baseline tumor tissue biopsy and archived primary prostate tissue, when able in a subset of subjects in both study groups.

(6) To compare clinical activity among subjects in Group 2 with DNA damage repair defects whose tumors are: (a) MSI-high only, (b) FA/BRCA signature positive only, or (c) both MSI-high and FA/BRCA signature positive.

4.0 BACKGROUND & RATIONALE

4.1 Background

In recent years, there has been significant enthusiasm surrounding tumor immunotherapy, specifically with immune checkpoint antibodies targeting the immune inhibitory co-receptors CTLA-4 and PD-1 (Postow MA et al., 2015). However, these agents have failed to demonstrate significant activity in patients with advanced prostate cancer (Kwon ED et al., 2014; Topalian SL et al., 2012). Dramatic and durable clinical responses were observed in approximately 10% of patients with mCRPC receiving CTLA-4 blockade (Kwek SS et al., 2015; Fong L et al., 2009). Furthermore, clinical responses in these trials have been shown to be associated with amplification of pre-existing immune responses (Kwek SS et al., 2012; Cha E et al., 2014).

Tumor associated mutations, which would provide a potential pool of neoantigens, have been shown to be associated with clinical responses to immune checkpoint inhibition. Mutational analysis in melanoma and NSCLC showed that greater mutational burden in the tumor is correlated with treatment response and survival benefit from immune checkpoint blockade (Snyder A et al., 2014; Rizvi NA et al., 2015). Consistent with this is the recently reported finding that patients with mismatch repair (MMR)-deficient metastatic carcinomas have high rates of somatic mutations, and have improved response and survival after PD-1 blockade with pembrolizumab (Le DT et al., 2015). One patient with MMR deficiency in this cohort had metastatic prostate cancer, and achieved complete response after treatment with pembrolizumab (Diaz LA et al., 2016).

Primary prostate cancers generally have a low mutational landscape (Alexandrov LB et al., 2013), which would presumably translate to a lower number of neoantigens that can potentially be recognized and targeted by the immune system. However, whole exome sequencing of metastatic prostate cancer indicates that the prevalence of MMR repair deficiency and microsatellite instability (MSI) in advanced prostate cancer can be as high as 12% (Pritchard CC et al., 2014). Furthermore, other mutations in the DNA repair pathway, specifically BRCA2, BRCA1 and ATM, have been reported to occur in approximately 19% of patients with advanced prostate cancer (Robinson D et al., 2015).

Recently, a 44 gene expression assay (DDRD IO) has been developed by Almac as a biomarker for defects in the Fanconi's anemia (FA)/BRCA pathway, and has been shown to predict response to DNA-damaging chemotherapy in patients with breast cancer (Mulligan JM et al., 2014). Multiple genes in this signature function in immune responses, including the immune checkpoint targets PD-L1 and IDO1 (Mulligan JM et al., 2014). Furthermore, positive FA/BRCA signature is correlated with intra-tumor lymphocyte infiltration, increased PD-L1 expression in tumor cells and lymphocytes, as well as microsatellite instability (unpublished data), making it an attractive biomarker to study for cancer immunotherapeutics.

This study is designed to test the efficacy of anti-PD-1 immunotherapy in patients with mCRPC who had received prior secondary hormonal therapy, using mutations in DNA repair genes, MSI status, and/or FA/BRCA signature as predictive biomarkers. A chemotherapy followed by re-challenge option is included to explore the theory that chemotherapy may enhance and recapture responses to subsequent immune checkpoint blockade.

Refer to the Investigator's Brochure (IB)/approved labeling for detailed background information on MK-3475.

4.1.1 Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades. 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 seems to correlate with improved prognosis and long-term survival in many solid tumors.

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). The structure of murine PD-1 has been resolved. 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. 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. PD-1 was shown to be expressed on activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B-cells, T regs and Natural Killer cells. Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells. The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types, including non-hematopoietic tissues as well as in various tumors. Both ligands are type I transmembrane receptors containing both IgV- and IgC-like domains in the extracellular region and contain short cytoplasmic regions with no known signaling motifs. Binding of either PD-1 ligand to PD-1 inhibits T-cell activation triggered through the T-cell receptor. PD-L1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments.

PD-L2 is thought to control immune T-cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T-cell function in peripheral tissues. Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor. PD-1 has been suggested to regulate tumor-specific T-cell expansion in subjects with melanoma (MEL). This suggests that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and should be considered as an attractive target for therapeutic intervention.

Pembrolizumab is a potent and highly selective humanized monoclonal antibody (mAb) of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Keytruda™ (pembrolizumab) has been approved in the United Stated for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilumumab and, if BRAF V600 mutation positive, a BRAF inhibitor. More recently, Keytruda was also approved for the treatment of non-small cell lung cancer (NSCLC) following progression on platinum-based chemotherapy in tumors that express PD-L1.

4.1.2 Preclinical and Clinical Trial Data

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

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

Metastatic castration resistant prostate cancer (mCRPC) represents the most advanced form of prostate cancer. While treatment options exist—including androgen receptor (AR)-targeted agents (abiraterone acetate and enzalutamide) and chemotherapy (docetaxel and cabazitaxel)—they are associated with significant toxicities, and resistance to these therapies eventually develop.

Immunotherapy is an attractive strategy for patients with advanced prostate cancer, because it has the potential to lead to durable responses and is generally better tolerated. However, the only FDA approved immunotherapy for prostate cancer to date is sipuleucel-T, an autologous cellular vaccine designed to stimulate an immune response targeting PAP (prostatic acid phosphatase) (Kantoff PW et al., 2010). The only phase 3 randomized controlled trial of immune checkpoint blockade, with ipilimumab in the mCRPC patients after docetaxel, failed to meet its primary endpoint of overall survival (Kwon ED et al., 2014). Early phase studies of PD-1 blockade in advanced malignancies has not demonstrated clinical activity in advanced prostate cancer (Topalian SL et al., 2012). Therefore, a need exists to improve immunotherapeutic strategies in this patient population.

Tumors that have defective DNA repair mechanisms have higher rates of spontaneous mutations, translating to higher expression of neoantigens that may be recognized by the immune system. In this study, we hypothesize that patients with mCRPC who harbor MMR-defective tumors and/or tumors that carry the 44-gene FA/BRCA expression signature (described in background) will have improved response to anti-PD-1 checkpoint blockade.

Half of the subjects enrolled will be selected to have intact MMR and negative FA/BRCA signature in their tumors, a phenotype that represents the majority of prostate cancer patients. The remaining subjects enrolled will be selected to harbor MSI-high and/or FA/BRCA signature in their tumors, which is anticipated to be present in approximately 20% of the target patient population. Thus we will enrich from the general mCRPC population. Patients with previously identified MSI-high tumor by PCR or IHC, or homozygous deletion or deleterious germline or somatic mutation(s) of DNA damage repair gene(s) (such as *BRCA1*, *BRCA2*, and *ATM)* identified in a CLIA-certified laboratory are allowed in the DNA damage repair defective group. All subjects will receive pembrolizumab.

4.2.2 Rationale for Dose Selection/Regimen/Modification

An open-label Phase I trial (Merck Protocol 001) is being conducted to evaluate the safety and clinical activity of single agent MK-3475. The dose escalation portion of this trial evaluated three dose levels, 1 mg/kg, 3 mg/kg, and 10 mg/kg, administered every 2 weeks (Q2W) in subjects with advanced solid tumors. All three dose levels were well tolerated and no dose-limiting toxicities were observed. This first in human study of MK-3475 showed evidence of target engagement and objective evidence of tumor size reduction at all dose levels (1 mg/kg, 3 mg/kg and 10 mg/kg Q2W). No MTD has been identified to date. Recent data from other clinical studies within the MK-3475 program has shown that a lower dose of MK-3475 and a less frequent schedule may be sufficient for target engagement and clinical activity.

PK data analysis of MK-3475 administered Q2W and Q3W showed slow systemic clearance, limited volume of distribution, and a long half-life (refer to IB). Pharmacodynamic data (IL-2 release assay) suggested that peripheral target engagement is durable (>21 days). This early PK and pharmacodynamic data provides scientific rationale for testing a Q2W and Q3W dosing schedule.

A population pharmacokinetic analysis has been performed using serum concentration time data from 476 patients. Within the resulting population PK model, clearance and volume parameters of MK-3475 were found to be dependent on body weight. The relationship between clearance and body weight, with an allometric exponent of 0.59, is within the range observed for other antibodies and would support both body weight normalized dosing or a fixed dose across all body weights. MK-3475 has been found to have a wide therapeutic range based on the melanoma indication. The differences in exposure for a 200 mg fixed dose regimen relative to a 2 mg/kg Q3W body weight based regimen are anticipated to remain well within the established exposure margins of 0.5 – 5.0 for MK-3475 in the melanoma indication. The exposure margins are based on the notion of similar efficacy and safety in melanoma at 10 mg/kg Q3W vs. the proposed dose regimen of 2 mg/kg Q3W (i.e. 5-fold higher dose and exposure). The population PK evaluation revealed that there was no significant impact of tumor burden on exposure. In addition, exposure was similar between the NSCLC and melanoma indications. Therefore, there are no anticipated changes in exposure between different indication settings.

The rationale for further exploration of 2 mg/kg and comparable doses of pembrolizumab in solid tumors is based on: 1) similar efficacy and safety of pembrolizumab when dosed at either 2 mg/kg or 10 mg/kg Q3W in melanoma patients, 2) the flat exposure-response relationships of pembrolizumab for both efficacy and safety in the dose ranges of 2 mg/kg Q3W to 10 mg/kg Q3W, 3) the lack of effect of tumor burden or indication on distribution behavior of pembrolizumab (as assessed by the population PK model) and 4) the assumption that the dynamics of pembrolizumab target engagement will not vary meaningfully with tumor type.

The choice of the 200 mg Q3W as an appropriate dose for the switch to fixed dosing is based on simulations performed using the population PK model of pembrolizumab showing that the fixed dose of 200 mg every 3 weeks will provide exposures that 1) are optimally consistent with those obtained with the 2 mg/kg dose every 3 weeks, 2) will maintain individual patient exposures in the exposure range established in melanoma as associated with maximal efficacy response and 3) will maintain individual patient exposures in the exposure range established in melanoma that are well tolerated and safe.

A fixed dose regimen will simplify the dosing regimen to be more convenient for physicians and to reduce potential for dosing errors. A fixed dosing scheme will also reduce complexity in the logistical chain at treatment facilities and reduce wastage.

4.2.3 Rationale for Endpoints

4.2.3.1 Efficacy Endpoints

Clinical efficacy endpoints for the primary and secondary objectives in the study include progression-free survival (rPFS, irPFS, and PFS), PSA response (any PSA decline and PSA decline ≥50% from baseline), and time to progression after taxane-based chemotherapy and pembrolizumab re-challenge.

4.2.3.2 **Biomarker Research**

The primary question in this study is whether MSI-high signature predict response to PD-1 blockade in patients with mCRPC. Correlative studies will be carried out to understand differential effects of these DNA damage repair biomarkers on the tumor microenvironment and immune response, at baseline and with treatment. Exploratory analysis will include:

1. Characterization and quantification of tumor-infiltrating lymphocytes (TILs)
2. Expression of PD-L1 in tumor cells and TILs
3. Quantification of TCR repertories
4. Assessment of tumoral mutational burden
5. Characterization of peripheral immune cell subsets

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

Metastatic castration resistant prostate cancer (mCRPC).

5.1.2 Subject Inclusion Criteria

In order to be eligible for participation in this trial, the subject must:

1. Documented histology of adenocarcinoma of the prostate.
2. Metastatic castration resistant prostate cancer with castrate-level testosterone (<50 ng/dL).
    a. Subjects must maintain a castrate-level testosterone during the study.
3. Disease progression defined by one or more of the following three criteria:
    a. PSA > 2.0 ng/mL and rising PSA by at least 2 consecutive measurements a minimum of 1-week apart.
    b. Soft tissue progression as defined by RECIST v1.1 criteria (Eisenhauer EA et al., 2009).
    c. Bone disease progression as defined by the Prostate Cancer Clinical Trials Working Group 3 (PCWG3) (Scher HI et al., 2016).
4. Have received prior secondary hormonal therapy including abiraterone, enzalutamide and/or apalutamide.
5. Be taking prednisone at a dose of ≤ 10mg/day, 7 days prior to starting treatment (C1D1).
6. Be willing and able to provide written informed consent/assent for the trial.
7. Be ≥ 18 years of age on day of signing informed consent.

8. Patients must agree to have a tumor tissue biopsy at baseline, and there must be a lesion that can be biopsied with acceptable clinical risk as judged by the investigator.

    a. Patients with inconclusive DNA damage repair status testing on this baseline biopsy must have one of the following (per the investigator's discretion):

        i. Sufficient archival tissue, or

        ii. An additional biopsy attempt.

    b. Patients with previously identified homozygous deletion or deleterious germline or somatic mutation(s) in DNA damage repair gene(s) (such as *BRCA1, BRCA2,* and *ATM)* identified in a CLIA-certified laboratory are allowed in Group 2.

        i. Somatic mutation(s) in DNA damage repair gene(s) needs to be identified on the biopsy of a castration-resistant tumor site.

        ii. Archival FFPE tissue will be requested for determination of MSI (if not already assessed by gene sequencing) signature status.

            1. A formalin-fixed paraffin-embedded (FFPE) tumor specimen in a paraffin block (preferred) or at least 10 slides containing unstained, freshly cut, serial sections must be available along with an associated pathology report before study enrollment.

        iii. If archival FFPE tissue is unable to be obtained or is insufficient, patients will be required to undergo tumor tissue biopsy if feasible for determination of MSI signature status.

c. Patients with germline mutation(s) in mismatch repair (MMR) gene(s) (i.e. Lynch syndrome), or have previously identified MSI-high tumor by PCR or MMR deficient tumor by IHC are also allowed in Group 2.

    i. Archival FFPE tissue will be requested for determination of FA/BRCA signature status.

        1. A formalin-fixed paraffin-embedded (FFPE) tumor specimen in a paraffin block (preferred) or at least 10 slides containing unstained, freshly cut, serial sections must be available along with an associated pathology report before study enrollment.

    ii. If archival FFPE tissue is unable to be obtained or is insufficient, patients will be required to undergo tumor tissue biopsy if feasible for determination of FA/BRCA signature status.

9. If group 1 is not filled, patients may proceed onto treatment without the completion of tests for DNA repair status. Once group 1 is filled, patients cannot be enrolled onto the study or start treatment until DNA damage repair status is successfully determined for study group placement.

    a. Patients will be replaced if they have tissues that are not evaluable for DNA repair mutations

10. Patients must be willing to provide archival tissue from prior biopsy or surgery for prostate cancer, if available.

    a. A formalin-fixed paraffin-embedded (FFPE) tumor specimen in a paraffin block (preferred) or at least 10 slides containing unstained, freshly cut, serial sections must be available along with an associated pathology report before study enrollment.

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

12. Patients must discontinue first generation antiandrogen therapy (i.e. bicalutamide, flutamide, and/or nilutamide at least 4-6 weeks prior to registration with no evidence of PSA decline after washout.

    a. Bicalutamide: Washout period at least 6 weeks

    b. Flutamide and nilutamide: Washout period at least 4 weeks

13. Patients must discontinue therapies for mCRPC, with the exception of GnRH agent, for 14 days, with the exception of anti-androgens with which there may be a withdrawal PSA response.

    a. Prior chemotherapy is allowed if no progression of disease on chemotherapy.

    b. Prior treatment with sipuleucel-T, radium-223, or PARP inhibitor (e.g. olaparib) is allowed.

    c. Tissue biopsy may be performed during washout period.

14. Demonstrate adequate organ function as defined below. All screening labs should be performed within 28 days of treatment initiation.

Table 1: Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1,500 /mcL
Platelets	≥100,000 / mcL
Hemoglobin	≥9 g/dL or ≥5.6 mmol/L without transfusion or EPO dependency (within 7 days of assessment)
Renal	
Serum creatinine **OR** Measured or calculated[a] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 X upper limit of normal (ULN) **OR** ≥60 mL/min for subject with creatinine levels > 1.5 X institutional ULN
Hepatic	
Serum total bilirubin	≤ 1.5 X ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 X ULN **OR** ≤ 5 X ULN for subjects with liver metastases
Albumin	≥2.5 mg/dL
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT) Activated Partial Thromboplastin Time (aPTT)	≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants ≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
[a]Creatinine clearance should be calculated per institutional standard.	

15. Male subjects of childbearing potential must agree to use an adequate method of contraception as outlined in Section 5.7.2 (Contraception), starting with the first dose of study therapy through 120 days after the last dose of study therapy.

Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject.

5.1.3 Subject Exclusion Criteria

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

1. Significant liver metastasis.

2. Prior taxane-based chemotherapy with progressive disease on chemotherapy.

    a. Prior docetaxel for metastatic hormone sensitive prostate cancer is allowed, if no progression of disease on docetaxel as defined by RECIST v1.1 and PCWG3.

    b. Prior taxane-based chemotherapy (i.e. docetaxel or cabazitaxel with or without platinum agent) for mCRPC is allowed if no progression of disease on chemotherapy as defined by RECIST v1.1 and PCWG3.

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

4. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy >10mg/day or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment.

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

6. Hypersensitivity to pembrolizumab or any of its excipients.

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

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

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

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

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

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

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

12. Has a history of (non-infectious) pneumonitis/interstitial lung disease that required steroids or has current pneumonitis/interstitial lung disease.

13. Has an active infection requiring systemic therapy.

14. 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.

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

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

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

18. Has a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).

19. Has known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected).

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

5.2 Trial Treatments

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

Table 2: Trial Treatment[1,2]

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

1. Trial treatment should begin on the day of study group assignment or as close as possible to the date on which study group is allocated/assigned.

2. Subjects who progress on pembrolizumab have the option of receiving taxane-based chemotherapy followed by repeat pembrolizumab for those who have a clinical response to chemotherapy. The patients will remain on study while receiving chemotherapy. A minimum of 2 cycles and a maximum of 8 cycles of chemotherapy will be given. The chemotherapy regimen will be at the discretion of the treating physician, and may consist of docetaxel or cabazitaxel with or without a platinum agent (e.g. carboplatin). Chemotherapy may be given with concurrent prednisone $\leq$ 10 mg/ day. Clinical response to chemotherapy is defined as PSA decrease by >50% or objective response by RECIST v1.1. Subjects who resume pembrolizumab after achieving response to chemotherapy should taper prednisone to $\leq$ 10 mg/day prior to restarting pembrolizumab.

5.2.1 Dose Selection/Modification

5.2.1.1 Dose Selection

The rationale for selection of doses to be used in this trial is provided in Section 4.0 – Background and Rationale.

Details on preparation and administration of pembrolizumab (MK-3475) are provided in the Pharmacy Manual.

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

Adverse events (both non-serious and serious) associated with pembrolizumab exposure may represent an immunologic etiology. These adverse events may occur shortly after the first dose or several months after the last dose of treatment. Pembrolizumab must be withheld for drug-related toxicities and severe or life-threatening AEs as per Table 3 below. See Section 5.6 for supportive care guidelines, including use of corticosteroids.

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Table 3: Dose Modification Guidelines for Drug-Related Adverse Events

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		

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Myocarditis	Grade 1	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 2, 3 or 4	Permanently discontinue		
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology 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,

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
pembrolizumab may be resumed. [e] Events that require discontinuation include, but are not limited to: encephalitis and other clinically important irAEs(vasculitis and sclerosing cholangitis).				

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 PI. The reason for interruption should be documented in the patient's study record.

5.2.2 Timing of Dose Administration

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

All trial treatments will be administered on an outpatient basis.

Pembrolizumab 200 mg will be administered as a 30 minute IV infusion every 3 weeks. A window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min).

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

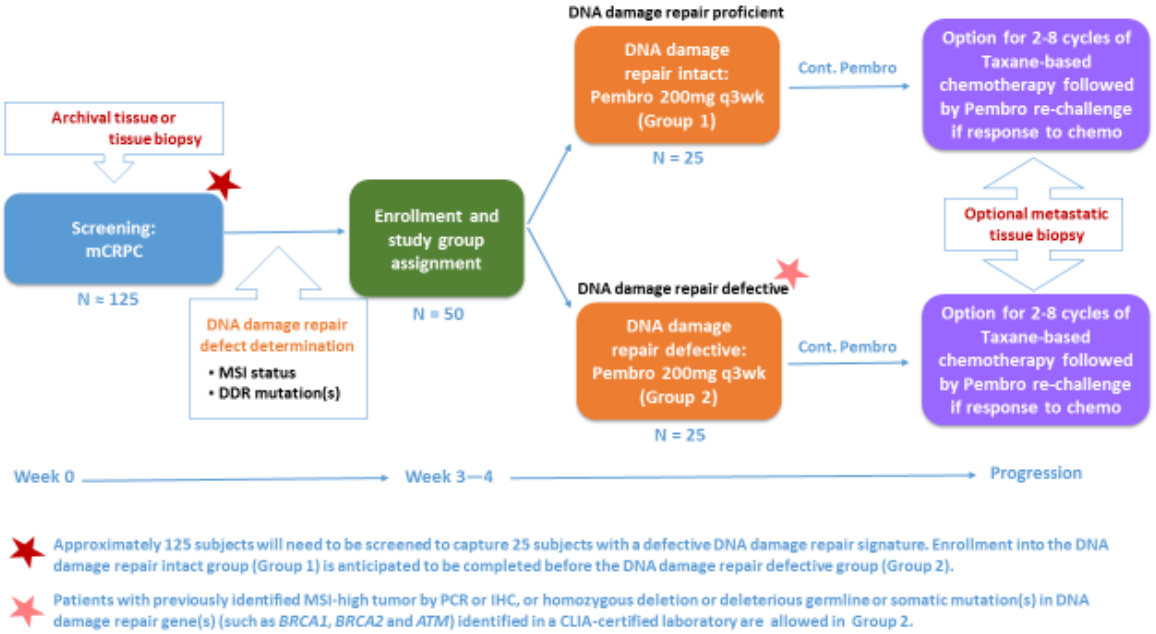
5.2.3 Trial Blinding/Masking

All subjects enrolled in this study will receive pembrolizumab. Subjects will not be blinded to their DNA damage repair signature status given efficacy of olaparib in mCRPC patients with BRCA1/2, ATM, Fanconi anemia, and CHEKC2 mutations (Mateo J et al., 2015).

5.3 Randomization or Treatment Allocation

Randomization will not be employed in this study due to the nature of the study. Subjects will be assigned to the appropriate study group based on DNA damage repair status (Group 1 if DNA repair gene unmutated/MMR intact; Group 2 if MSI-high and/or DNA repair gene mutated). All subjects enrolled will receive pembrolizumab. Patients with previously identified MSI-high tumor by PCR or HIC, or homozygous deletion or deleterious somatic mutation(s) in DNA damage repair gene(s) (such as *BRCA1*, *BRCA2* and *ATM*) identified in a CLIA-certified laboratory are allowed in Group 2 (Figure 1).

Figure 1: Study schema



5.4 Concomitant Medications/Vaccinations (allowed & prohibited)

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

5.4.1 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. All concomitant medication will be recorded on the case report form (CRF) including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the CRF.

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

5.4.2 Prohibited Concomitant Medications

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

- Antineoplastic systemic chemotherapy or biological therapy
    - Exception: Androgen deprivation therapy (ADT). Patients are required to maintain castrate-level testosterone (<50 ng/dL) with a GNRH agonist or antagonist +/- LHRH. Patients without history of bilateral orchiectomy are required to remain on ADT.
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab
- Radiation therapy
    - Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed at the investigator's discretion.
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine.
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. Glucocorticoids without significant systemic bioavailability (e.g. budesonide or joint injections) are allowed. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.

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.

The Exclusion Criteria describes other medications which are prohibited in this trial.

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

5.5 Rescue Medications & Supportive Care

5.5.1 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. 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 does not need to follow the treatment guidance (as outlined below). Refer to Section 5.2.1 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.

- **Pneumonitis**:
    - For **Grade 2 events**, treat with systemic corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
    - For **Grade 3-4 events**, immediately treat with intravenous steroids. Administer additional anti-inflammatory measures, as needed.
    - Add prophylactic antibiotics for opportunistic infections in the case of prolonged steroid administration.

- **Diarrhea/Colitis**:

  Subjects should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus).

  - All subjects who experience 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. For Grade 2 or higher diarrhea, consider GI consultation and endoscopy to confirm or rule out colitis.
  - For **Grade 2 diarrhea/colitis,** administer oral corticosteroids.
  - For **Grade 3 or 4 diarrhea/colitis,** treat with intravenous steroids followed by high dose oral steroids.
  - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

- **Type 1 diabetes mellitus (if new onset, including diabetic ketoacidosis [DKA]) or ≥ Grade 3 Hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis (DKA)**
  - For **T1DM** or **Grade 3-4** Hyperglycemia
    - Insulin replacement therapy is recommended for Type I diabetes mellitus and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria.
    - Evaluate patients with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.

- **Hypophysitis**:
  - For **Grade 2** events, treat with corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
  - For **Grade 3-4** events, treat with an initial dose of IV corticosteroids followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

- **Hyperthyroidism or Hypothyroidism**:

  Thyroid disorders can occur at any time during treatment. Monitor patients for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders.

  - **Grade 2** hyperthyroidism events (and **Grade 2-4** hypothyroidism):
    - In hyperthyroidism, non-selective beta-blockers (e.g. propranolol) are suggested as initial therapy.
    - In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyroinine, is indicated per standard of care.
  - **Grade 3-4** hyperthyroidism
    - Treat with an initial dose of IV corticosteroid followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

- **Hepatic**:
  - For **Grade 2** events, monitor liver function tests more frequently until returned to baseline values (consider weekly).
    - Treat with IV or oral corticosteroids
  - For **Grade 3-4** events, treat with intravenous corticosteroids for 24 to 48 hours.
  - When symptoms improve to Grade 1 or less, a steroid taper should be started and continued over no less than 4 weeks.

- **Renal Failure or Nephritis**:
  - For Grade 2 events, treat with corticosteroids.
  - For Grade 3-4 events, treat with systemic corticosteroids.
  - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

- **Management of Infusion Reactions**: Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion.

  Table 4 below shows treatment guidelines for subjects who experience an infusion reaction associated with administration of pembrolizumab (MK-3475).

Table 4: Infusion Reaction 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 subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for < =24 hrs	**Stop Infusion and monitor symptoms.** 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 subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within one 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 subject should be premedicated for the next scheduled dose. **Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.**	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab (MK-3475) with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic).
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: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **Subject is permanently discontinued from further trial treatment administration.**	No subsequent dosing
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.		

5.6 Diet/Activity/Other Considerations

5.6.1 Diet

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

5.6.2 Contraception

Pembrolizumab may have adverse effects on a fetus in utero. Furthermore, it is not known if pembrolizumab has transient adverse effects on the composition of sperm.

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

Acceptable methods of contraception are:

Single method (one of the following is acceptable):

- Intrauterine device (IUD) for subject's partner
- Vasectomy
- Contraceptive rod implanted into the skin for subject's partner

Combination method (requires use of two of the following):

- Diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide) for subject's partner
- Cervical cap with spermicide (for subject's partner, nulliparous women only)
- Contraceptive sponge (for subject's partner, nulliparous women only)
- Male condom or female condom (cannot be used together)
- Hormonal contraceptive: oral contraceptive pill (estrogen/progestin pill or progestin-only pill), contraceptive skin patch, vaginal contraceptive ring, or subcutaneous contraceptive injection (for subject's partner)

Abstinence (relative to heterosexual activity) can be used as the sole method of contraception if it is consistently employed as the subject's preferred and usual lifestyle and if considered acceptable by local regulatory agencies and ERCs/IRBs. Periodic abstinence (e.g., calendar, ovulation, sympto-thermal, post-ovulation methods, etc.) and withdrawal are not acceptable methods of contraception.

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study subjects of childbearing potential must adhere to the contraception requirement (described above) from the day of study medication initiation (or 14 days prior to the initiation of study medication for oral contraception) throughout the study period up to 120 days after the last dose of trial therapy. If there is any question that a subject of childbearing potential will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

5.6.3 Use in Pregnancy

If a subject impregnates his female partner, the study personnel must be informed immediately and the pregnancy reported to Merck and followed as described above and in Section 7.2.2.

5.7 Subject Withdrawal/Discontinuation Criteria

Subjects may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn by the investigator or the Sponsor if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding discontinuation or withdrawal are provided in Section 7.1.4 – Other Procedures.

A subject must be discontinued from the trial for any of the following reasons:

- The subject or legal representative (such as a parent or legal guardian) withdraws consent.
- Confirmed radiographic disease progression

  Note: For unconfirmed radiographic disease progression, please see Section 5.2.2

  Note: A subject may be granted an exception to continue on treatment with confirmed radiographic progression if clinically stable or clinically improved. See Section 7.1.2.2.
- Unacceptable adverse experiences as described in Section 5.2.1.2
- Intercurrent illness that prevents further administration of treatment
- Investigator's decision to withdraw the subject
- Noncompliance with trial treatment or procedure requirements
- The subject is lost to follow-up
- Completed 24 months of uninterrupted treatment with pembrolizumab or 35 administrations of study medication, whichever is later.

  Note: 24 months of study medication is calculated from the date of first dose. Subjects who stop pembrolizumab after 24 months may be eligible for up to one year of additional study treatment if they progress after stopping study treatment provided they meet the requirements detailed in Section 7.1.7.5
- Administrative reasons

The End of Treatment and Follow-up visit procedures are listed in Section 6 (Protocol Flow Chart) and Section 7.1.2 (Treatment Period). After the end of treatment, each subject will be followed for 30 days for adverse event monitoring (serious adverse events will be collected for 90 days after the end of treatment as described in Section 7.2.3.1). Subjects who discontinue for reasons other than progressive disease will have post-treatment follow-up for disease status until disease progression, initiating a non-study cancer treatment, withdrawing consent or becoming lost to follow-up. After documented disease progression each subject will be followed by telephone for overall survival until death, withdrawal of consent, or the end of the study, whichever occurs first.

5.7.1 Discontinuation of Study Therapy after CR

Discontinuation of treatment may be considered for subjects who have attained a confirmed CR that have been treated for at least 24 weeks with pembrolizumab and had at least two treatments with pembrolizumab beyond the date when the initial CR was declared. Subjects who then experience radiographic disease progression may be eligible for up to one year of additional treatment with pembrolizumab via the Second Course Phase at the discretion of the investigator if no cancer treatment was administered since the last dose of pembrolizumab, the subject meets the safety parameters listed in the Inclusion/Exclusion criteria, and the trial is open. Subjects will resume therapy at the same dose and schedule at the time of initial discontinuation. Additional details are provided in Section 7.1.7.5.

5.8 Subject Replacement Strategy

All patients who receive any study therapy will be analyzed for safety and efficacy. Subjects who discontinue from study participation prior to receiving any study therapy may be replaced after discussion with the Study Monitor. Subjects who have received any dose of study therapy will not be replaced. Patients removed from study for unacceptable treatment related adverse event(s) will be followed until resolution or stabilization of all treatment related AEs to Grade 0-1 or until the beginning of a new anti-neoplastic therapy, whichever occurs first. However, they will not be replaced.

5.9 Stopping Rule

A stopping rule for safety will halt accrual to the study and prompt reevaluation of pembrolizumab dose if unacceptable treatment-related toxicity (defined as any Grade 4 toxicity, any recurrent Grade 3 toxicity, or any Grade 3 toxicity persisting more than 4 weeks) is observed at a frequency of ≥33% in any study group. Because pembrolizumab is generally well tolerated, this safety review will occur after a total of 9 subjects have been accrued (either study group).

5.10 Clinical Criteria for Early Trial Termination

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

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

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

6.0 TRIAL FLOW CHART

Trial Period:	**Screening Phase**		**Treatment Cycles[1]**	**Treatment at Progression[2]**		**End of Treatment**	**Post-Treatment**		
Treatment Cycle/Title:	Pre-screening (Visit 1)	Main Study Screening (Visit 2)	Pembrolizumab	Taxane-based Chemo	Post-chemotherapy Pembrolizumab	Discontinuation	Safety Follow-up[3]	Follow Up Visits[4]	Survival Follow-Up[5]
Scheduling Window (Days):		-28 to -1	Every 21 days ± 3 days	Every 21 days +3 days x 2-8	Every 21 days ± 3 days	At time of Discontinuation	30 days post discontinuation	Every 12 weeks post discontinuation	Every 12 weeks
Administrative Procedures									
Pre-screening Consent[6]	x								
Informed Consent		x							
Inclusion/Exclusion Criteria		x							
Demographics and Medical History		x							
Prior and Concomitant Medication Review		x							
Pembrolizumab Administration			x		x				
Chemotherapy Administration[7]				x					
Post-study anticancer therapy status								x	x
Survival Status									x
Clinical Procedures/Assessments									
Review Adverse Events			x	x[8]	x	x	x		
Full Physical Examination		x							
Directed Physical Examination			x	x	x	x	x	x	
Vital Signs and Weight[9]		x	x	x	x	x	x	x	
ECOG Performance Status		x	x	x	x	x			

Trial Period:	**Screening Phase**		**Treatment Cycles[1]**	**Treatment at Progression[2]**		**End of Treatment**	**Post-Treatment**		
Treatment Cycle/Title:	Pre-screening (Visit 1)	Main Study Screening (Visit 2)	Pembrolizumab	Taxane-based Chemo	Post-chemotherapy Pembrolizumab	Discontinuation	Safety Follow-up[3]	Follow Up Visits[4]	Survival Follow-Up[5]
Scheduling Window (Days):		-28 to -1	Every 21 days ± 3 days	Every 21 days +3 days x 2-8	Every 21 days ± 3 days	At time of Discontinuation	30 days post discontinuation	Every 12 weeks post discontinuation	Every 12 weeks
Laboratory Procedures/Assessments: analysis performed by LOCAL laboratory[10]									
PT/INR and aPTT		x							
CBC with Differential[11]		x	x	x	x	x			
Comprehensive Serum Chemistry[12]		x	x	x	x	x			
Urinalysis		x							
LDH		x	x	x	x	x			
TSH[13]		x	x	x	x	x			
Efficacy Measurements									
Tumor Imaging		x[14]	x[14]	x[14]	x[14]	x[14]		x[14]	
PSA[15]		x	x	x	x	x		x	
Tumor Biopsies/Archival Tissue Collection/Correlative Studies Blood									
Newly Obtained Tissue Biopsy[16]	x			x	x				
Mutation/MSI testing[16]	x			x	x				
FA/BRCA signature testing[16]	x			x	x				
Archival Tissue Collection[17]		x							
Immunomonitoring Blood Collection[18]		x	x	x	x	x	x	x	

1. Pembrolizumab 200mg IV every 3 weeks until confirmed progression of disease by irRC, clinical deterioration, or unacceptable toxicity.
2. Subjects who progress on initial pembrolizumab treatment have the option of undergoing biopsy of a metastatic site and/or receiving taxane-based chemotherapy for 2 to 8 cycles, if deemed fit by the investigator and subject. For site of metastatic biopsy, preferences will be given to repeat biopsy of metastatic bone tissue that was sampled at baseline or demonstrated radiographic progression on pembrolizumab, whenever feasible. If a bone biopsy is not feasible, then a soft tissue or lymph node biopsy may be performed. Repeat progression biopsy should be obtained prior to subsequent treatment. Subjects who respond to chemotherapy (defined as achieving objective response by RECIST v1.1 or PSA decline by >50%) have the option of repeating pembrolizumab, assuming adequate performance status and organ functions as specified in the inclusion criteria. Pembrolizumab should be restarted within 30 days of the last dose of chemotherapy. Prednisone should be tapered to ≤ 10 mg/day prior to restarting pembrolizumab. Subjects who reinitiate pembrolizumab following chemotherapy will have the option of undergoing an additional biopsy of the metastatic site. Additional biopsy should be obtained within 30 days of reinitiating pembrolizumab.
3. The mandatory Safety Follow-Up Visit should be conducted approximately 30 days after the last dose of trial treatment or before the initiation of a new anti-cancer treatment, whichever comes first (See Section 7.1.7.3.1).
4. Subjects who discontinue pembrolizumab for a reason other than disease progression will move into the Follow-Up Phase and should be assessed every 12 weeks (± 7 days) by radiologic imaging to monitor disease status. Every effort should be made to collect information regarding disease status until the start of new anti-neoplastic therapy, disease progression, death, end of the study or if the subject begins retreatment with pembrolizumab as detailed in Section 7.1.7.5. Information regarding post-study anti-neoplastic treatment will be collected if new treatment is initiated.
5. Once a subject experiences confirmed disease progression or starts a new anti-cancer therapy, the subject moves into the survival follow-up phase and should be contacted by telephone every 12 weeks to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first (See Section 7.1.7.4.1).
6. Pre-screening consent for tissue biopsy for mutational sequencing and MSI testing.
7. Subjects who progress on pembrolizumab in either study group will have the option of receiving taxane-based chemotherapy followed by repeat pembrolizumab for those who have a clinical response to chemotherapy. Chemotherapy should be started within 60 days of last dose of pembrolizumab. Chemotherapy regimen will be at the discretion of the treating physician, and may consist of docetaxel or cabazitaxel with or without a platinum agent (e.g. carboplatin). A minimum of 2 cycles and a maximum of 8 cycles of chemotherapy will be given. Clinical response to chemotherapy is defined as PSA decrease by >50% or objective response by RECIST v1.1. Chemotherapy may be given with prednisone ≤ 10 mg/day. Prednisone should be tapered to ≤ 10 mg/day prior to restarting pembrolizumab.
8. Adverse events documented during administration of chemotherapy will not be attributed to pembrolizumab, unless they are determined to be irAEs by the investigator.
9. Vital signs should include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at screening only.
10. Labs may be collected within a window of up to 3 days prior to each dosing of pembrolizumab.
11. CBC includes RBC count, hemoglobin, hematocrit, WBC count with automated differential (neutrophils, lymphocytes, eosinophils, monocytes, basophils, and other cells), and platelet count. A manual differential can be done if clinically indicated.
12. Comprehensive serum chemistry includes sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, calcium, total bilirubin, ALT, AST, alkaline phosphatase, total protein, and albumin.
13. T3 and FT4 should be checked if TSH is outside the normal range.

14. Radiographic evaluations and tumor measurements will be performed at screening 28 days prior to C1D1, then every 12 weeks (+/- 2 weeks) thereafter, including the off study evaluation. During post-chemotherapy pembrolizumab, radiographic evaluation and tumor measurements will be performed every 12 weeks (+/- 2 weeks). Weeks are in reference to calendar week, and should not be adjusted for pembrolizumab dosing delays. CT chest/abdomen/pelvis with contrast and bone scan should be performed. If sodium fluoride (NaF) PET/CT was initially used for staging, the same bone imaging modality (i.e. NaF PET/CT) should be used throughout the study. See Section 7.1.4.6.
15. Subjects will check PSA at time of screening, and then every 3 weeks (+/- 1 week), including the off study evaluation. Weeks are in reference to calendar week, and should not be adjusted for pembrolizumab dosing delays.
16. Subjects will undergo biopsy of any lesion (primary or metastatic) at the time of screening for mutational sequencing / MSI testing. MSI testing will be performed at UCSF (See Laboratory Manual). FA/BRCA expression signature will be assessed retrospectively.
17. Archival prostate biopsy or surgical tissue will be requested if available. a. A formalin-fixed paraffin-embedded (FFPE) tumor specimen in a paraffin block (preferred) or at least 10 slides containing unstained, freshly cut, serial sections must be available along with an associated pathology report before study enrollment.
18. Blood will be collected in four 10mL BD Sodium Heparin^{N} (NH) 158 USP Units Plus Blood Collection Tubes (green-top) and sent to the Immune Monitoring Core at UCSF (See Section 7.1.5.1.2).

7.0 TRIAL PROCEDURES

7.1 Trial Procedures

The Trial Flow Chart - Section 6.0 summarizes the trial procedures to be performed at each visit. The study-specific assessments are detailed below (Section 7.1.1 and Section 7.1.2). Screening assessments must be performed within 28 days prior to the first dose of investigational product. Any results falling outside of the reference ranges may be repeated at the discretion of the investigator. All on-study visit procedures are allowed a window of ± 3 days unless otherwise noted. Treatment or visit delays for public holidays or weather conditions do not constitute a protocol violation.

Individual trial procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator.

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

7.1.1 Pretreatment Period

7.1.1.1 Screening Assessments

The Screening procedures and assessments, except for biopsy and archival tissue collection, must be completed within 28 days of the Day 1 Visit.

- Physical examination
- Vital signs and weight
- Complete medical history and demographics
- Baseline conditions assessment
- Documentation of disease assessment
- Performance status
- Baseline medications taken within 28 days of Day 1
- Sample of tumor tissue
- Complete blood count (CBC) with differential and platelet count including
    - RBC count, hemoglobin, hematocrit, WBC count with automated differential (neutrophils, lymphocytes, eosinophils, monocytes, basophils, and other cells), and platelet count. A manual differential can be done if clinically indicated.
- Blood chemistry assessment including
    - Sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, calcium, total bilirubin, ALT, AST, alkaline phosphatase, total protein, and albumin

- Thyroid function tests: thyroid-stimulating hormone (TSH)
  - T3 and FT4 should be checked if TSH is outside the normal range
- Coagulation assessment, including prothrombin time, partial thromboplastin time, international normalized ratio (PT/PTT/INR)
- LDH
- PSA
- Immune monitoring blood collection
- Urinalysis
- Tumor imaging
  - CT chest/abdomen/pelvis with contrast
  - Bone scan - If sodium fluoride (NaF) PET/CT was initially used for staging, the same bone imaging modality (i.e. NaF PET/CT) should be used throughout the study
- Biopsy of lesion at the time of screening for mutational testing and MSI testing.
  - Soft tissue or lymph node biopsies will be prioritized. If a soft tissue or lymph node biopsy is not feasible, then a bone biopsy may be performed.
- Archival tissue collection, if available

7.1.2 Treatment Period

7.1.2.1 **Every 21 days**

- Directed physical examination
- Vital signs and weight
- Performance status
- Evaluation of adverse events
- CBC with differential and platelet count
- Blood chemistry assessment
- Thyroid function tests
- LDH
- PSA - every 3 weeks (+/- 1 week), including the off study evaluation. Weeks are in reference to calendar week, and should not be adjusted for pembrolizumab dosing delays.
- Immune monitoring blood collection

- Tumor imaging - Radiographic evaluations and tumor measurements will be performed at screening (within 28 days prior to the first dose of pembrolizumab), then every 12 weeks (+/- 2 weeks) thereafter, including the off study evaluation. During post-chemotherapy pembrolizumab, radiographic evaluation and tumor measurements will be performed every 12 weeks (+/- 2 weeks). Weeks are in reference to calendar week, and should not be adjusted for pembrolizumab dosing delays.
- Pembrolizumab administration - 200mg IV every 3 weeks until confirmed progression of disease by irRC, clinical deterioration, or unacceptable toxicity

7.1.2.2 **Optional Treatment at Progression**

Subjects who progress on initial pembrolizumab treatment have the option of undergoing biopsy of a metastatic site and/or receiving taxane-based chemotherapy for 2 to 8 cycles, if deemed fit by the investigator and subject. For site of metastatic biopsy, preferences will be given to repeat biopsy of metastatic bone tissue that was sampled at baseline or demonstrated radiographic progression on pembrolizumab, whenever feasible. If a bone biopsy is not feasible, then a soft tissue or lymph node biopsy may be performed. Repeat progression biopsy should be obtained prior to subsequent treatment. The chemotherapy regimen will be at the discretion of the treating physician, and may consist of docetaxel or cabazitaxel with or without a platinum agent (e.g. carboplatin). The doses of chemotherapy may be modified at the discretion of the investigator as clinically indicated. Chemotherapy may be given with concurrent prednisone $\leq$ 10mg/day. Patients will remain on study while receiving chemotherapy, and chemotherapy should be started within 30 days of the last dose of pembrolizumab. Subjects should be re-imaged every 12 weeks on chemotherapy. Subjects who respond to chemotherapy (defined as achieving objective response by RECIST v1.1 or PSA decline by >50%) have the option of repeating pembrolizumab, assuming adequate performance status and organ functions as specified in the inclusion criteria. Pembrolizumab should be restarted within 30 days of the last dose of chemotherapy. Prednisone should be tapered to $\leq$ 10mg/day prior to restarting pembrolizumab. Subjects who reinitiate pembrolizumab following chemotherapy will have the option of undergoing an additional biopsy of the metastatic site. Additional biopsy should be obtained within 30 days of reinitiating pembrolizumab.

7.1.2.2.1 Taxane-based chemotherapy - Every 21 Days (for 2-8 cycles)

- Directed physical examination
- Vital signs and weight
- Performance status
- Evaluation of adverse events
- CBC with differential and platelet count
- Blood chemistry assessment
- Thyroid function tests
- LDH
- PSA - every 3 weeks (+/- 1 week), including the off study evaluation. Weeks are in reference to calendar week, and should not be adjusted for pembrolizumab dosing delays.
- Immune monitoring blood collection
- Tumor imaging – every 12 weeks
- Chemotherapy administration

7.1.2.2.2 Post-Chemotherapy Pembrolizumab - Every 21 days

- Directed physical examination
- Vital signs and weight
- Performance status
- Evaluation of adverse events
- CBC with differential and platelet count
- Blood chemistry assessment
- Thyroid function tests
- LDH
- PSA - every 3 weeks
- Immune monitoring blood collection
- Tumor imaging – every 12 weeks
- Pembrolizumab administration

7.1.2.3 **End of Treatment**

At time of discontinuation of study treatment:

- Directed physical examination
- Vital signs and weight
- Performance status
- Evaluation of adverse events
- CBC with differential and platelet count
- Blood chemistry assessment
- Thyroid function tests
- LDH
- PSA
- Immune monitoring blood collection
- Tumor imaging

7.1.2.4 **Post-Treatment**

7.1.2.4.1 Safety Follow-up

30 days post study treatment discontinuation:

- Directed physical examination
- Vital signs and weight
- Evaluation of adverse events
- Immune monitoring blood collection

7.1.2.4.2 Follow-up Visits

Subjects who discontinue pembrolizumab for a reason other than disease progression will move into the Follow-Up Phase and should be assessed every 12 weeks (± 7 days) by radiologic imaging to monitor disease status. Every effort should be made to collect information regarding disease status until the start of new anti-neoplastic therapy, disease progression, death, end of the study or if the subject begins retreatment with pembrolizumab as detailed in Section 7.1.2.2. Information regarding post-study anti-neoplastic treatment will be collected if new treatment is initiated.

Post discontinuation, every 12 weeks:

- Post-study anticancer therapy status
- Directed physical examination
- Vital signs and weight
- Immune monitoring blood collection
- Tumor imaging
- PSA

7.1.2.4.3 Survival Follow-up

Once a subject experiences confirmed disease progression or starts a new anti-cancer therapy, the subject moves into the survival follow-up phase and should be contacted by telephone every 12 weeks to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

7.1.3 Administrative Procedures

7.1.3.1 Informed Consent

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

7.1.3.1.1 General 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.

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

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

7.1.3.2 **Inclusion/Exclusion Criteria**

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

7.1.3.3 **Medical History**

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

7.1.3.4 **Prior and Concomitant Medications Review**

7.1.3.4.1 Prior Medications

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

7.1.3.4.2 Concomitant Medications

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

7.1.3.5 **Disease Details and Treatments**

7.1.3.5.1 Disease Details

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

7.1.3.5.2 Prior Treatment Details

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

7.1.3.5.3 Subsequent Anti-Cancer Therapy Status

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

7.1.3.6 **Assignment of Screening Number**

All patients who are consented will be registered in OnCore®, the UCSF Helen Diller Family Comprehensive Cancer Center Clinical Trial Management System (CTMS). The system is password protected and meets HIPAA requirements. All patients will have a unique identification number.

7.1.3.7 **Assignment of Study Group Number**

Patients enrolled into the study will be assigned to Group 1 or Group 2 based on DNA damage repair status determined by MSI and/or mutational sequencing (e.g. UCSF500, Foundation, Strata). Study group assignment will be documented in OnCore®.

7.1.3.8 **Trial Compliance (Medication/Diet/Activity/Other)**

A subject may be discontinued from the study for significant non-compliance with treatment or procedure requirements.

7.1.4 Clinical Procedures/Assessments

7.1.4.1 **Adverse Event (AE) Monitoring**

The investigator or qualified designee will assess each subject to evaluate for potential new or worsening AEs as specified in the Trial Flow Chart and more frequently if clinically indicated. Adverse experiences will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE Version 4.0 (see Appendix 11.2). Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

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

7.1.4.2 **Full Physical Exam**

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

7.1.4.3 **Directed Physical Exam**

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

7.1.4.4 **Vital Signs**

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

7.1.4.5 **Eastern Cooperative Oncology Group (ECOG) Performance Scale**

The investigator or qualified designee will assess ECOG status (see Appendix 11.1) at screening, prior to the administration of each dose of trial treatment and discontinuation of trial treatment as specified in the Trial Flow Chart.

7.1.4.6 **Tumor Imaging and Assessment of Disease**

Radiographic evaluations and tumor measurements will be performed at screening (within 28 days prior to the first dose of pembrolizumab), then every 12 weeks (+/- 2 weeks) thereafter, including the off study evaluation. Weeks are in reference to calendar week, and should not be adjusted for pembrolizumab dosing delays.

CT chest/abdomen/pelvis with contrast and bone scan should be performed. If sodium fluoride (NaF) PET/CT was initially used for staging, the same bone imaging modality (i.e. NaF PET/CT) should be used throughout the study.

Immune-related response criteria (irRC) will be used to determine radiographic response of non-bone tissue on pembrolizumab. PCWG3 will be used to determine radiographic response of bone metastases on pembrolizumab; specifically the appearance of 2 or more new bone lesions will qualify as disease progression. For subjects who progress and go on to receive taxane-based chemotherapy,) RECIST v1.1 and/or PCWG3 will be used to determine radiographic response on chemotherapy.

7.1.4.7 **Tumor Tissue Collection and Correlative Studies Blood Sampling**

Subjects will undergo tumor tissue biopsy at the time of screening for DNA repair defects. Assays that can be used for detecting this include: targeted mutation sequencing and MSI testing. Targeted mutation sequencing can include the UCSF 500 as well as commercial tests (e.g. Foundation, Strata). MSI testing will be performed at UCSF if the targeted mutation sequencing is equivocal. FA/BRCA signature testing will be performed retrospectively by Almac or other equivalent platform.

Archival tissues

Patients with previously identified DNA repair defects will have archival tumor tissue requested (See Section 5.1.2). A formalin-fixed paraffin-embedded (FFPE) tumor specimen in a paraffin block (preferred) or at least 10 slides containing unstained, freshly cut, serial sections must be available along with an associated pathology report before study enrollment. If archival FFPE tissue is unable to be obtained or is insufficient, patients will be required to undergo tumor tissue biopsy if feasible, for determination of DNA repair mutations, MSI and/or FA/BRCA signature status.

Archival prostate biopsy or surgical tissue will also be requested if available. A formalin-fixed paraffin-embedded (FFPE) tumor specimen in a paraffin block (preferred) or at least 10 slides containing unstained, freshly cut, serial sections must be available along with an associated pathology report before study enrollment.

Peripheral blood immune monitoring

Blood will be collected in four 10mL BD Sodium Heparin^{N} (NH) 158 USP Units Plus Blood Collection Tubes (green-top) and sent to the Immune Monitoring Core at UCSF (See Section 7.1.5.1.2).

7.1.5 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below. Laboratory tests for hematology, chemistry, urinalysis, and others are specified in Table 5.

Table 5: Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Blood	PT (INR)
Hemoglobin	Alkaline phosphatase	Glucose	aPTT
Platelet count	Alanine aminotransferase (ALT)	Protein	Total thriiodothyronine (T3)
WBC (total and differential)	Aspartate aminotransferase (AST)	Specific gravity	Free tyroxine (T4)
Red Blood Cell Count	Lactate dehydrogenase (LDH)	Microscopic exam *(If abnormal results are noted)*	Thyroid stimulating hormone (TSH)
Absolute Neutrophil Count	Carbon Dioxide †		Blood for correlative studies
Absolute Lymphocyte Count	*(CO_2 or biocarbonate)*		
	Calcium		
	Chloride		
	Glucose		
	Potassium		
	Sodium		
	Total Bilirubin		
	Total protein		
	Creatinine		
	Blood Urea Nitrogen		

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

7.1.5.1 **Biomarker Determination and Correlative Studies**

7.1.5.1.1 Tissue Biopsy and DNA Damage Repair Status Evaluation

MSI testing will be performed by the pathology department at UCSF. FA/BRCA signature testing will be performed by Almac or other equivalent platform. Sample collection, processing, storage and shipment instructions for tissue samples will be detailed in the Laboratory Manual.

7.1.5.1.2 Blood for Immunomonitoring

At the indicated time points in the trial flow chart (Section 6.0), blood will be collected in four 10mL BD Sodium Heparin^{N} (NH) 158 USP Units Plus Blood Collection Tubes (green-top) and sent to the Immune Monitoring Core at UCSF.

Immune Monitoring Core
University of California, San Francisco
[redacted].
San Francisco, CA 94143
[redacted]

7.1.6 Other Procedures

7.1.6.1 **Withdrawal/Discontinuation**

When a subject discontinues/withdraws prior to trial completion, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.2 - Assessing and Recording Adverse Events.

Subjects who a) attain a CR or b) complete 24 months of treatment with pembrolizumab may discontinue treatment with the option of restarting treatment if they meet the criteria specified in Section 7.1.7.5. After discontinuing treatment following assessment of CR, these subjects should return for a Safety Follow-up Visit and then proceed to the Follow-Up Period of the study (described in Section 7.1.2.4).

7.1.6.2 **Blinding/Unblinding**

All subjects enrolled in this study will receive pembrolizumab. Subjects will not be blinded to their DNA damage repair signature status given efficacy of olaparib in mCRPC patients with BRCA1/2, ATM, Fanconi anemia, and CHEK2 mutations (Mateo J et al., 2015).

7.1.7 Visit Requirements

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

7.1.7.1 **Screening**

7.1.7.1.1 Screening Period

During the initial accrual onto the clinical trial, patients without the full results of DNA repair status testing being available may be enrolled onto the clinical trial and started on treatment so long as there are available slots in Group 1 and so long as we have biopsy material to perform the testing. Once Group 1 is filled and all subjects have had their DNA repair status verified, the study will only enroll to Group 2. These subjects must be screened for DNA repair defective status before being enrolled.

Subjects will undergo two screening visits. In the pre-screening visit (Visit 1), a pre-screening consent for tumor tissue biopsy for mutational sequencing and MSI testing will be obtained. Subjects will move into the main study screening visit (Visit 2), at which time informed consent for the study will be obtained, and study procedures outlined in Section 7.1, including labs and imaging, as will be performed.

7.1.7.2 **Treatment Period**

During the treatment period, subjects will undergo required study procedures as indicated in Section 7.1. All subjects should have vital checked, a focused physical exam, adverse events reviewed, laboratory reviewed, and relevant imaging results reviewed before receiving the next planned dose of pembrolizumab.

7.1.7.3 **Post-Treatment Visits**

7.1.7.3.1 Safety Follow-Up Visit

The mandatory Safety Follow-Up Visit should be conducted approximately 30 days after the last dose of trial treatment or before the initiation of a new anti-cancer treatment, whichever comes first. All AEs that occur prior to the Safety Follow-Up Visit should be recorded. Subjects with an AE of Grade > 1 will be followed until the resolution of the AE to Grade 0-1 or until the beginning of a new anti-neoplastic therapy, whichever occurs first. SAEs that occur within 90 days of the end of treatment or before initiation of a new anti-cancer treatment should also be followed and recorded. Subjects who are eligible for retreatment with pembrolizumab (as described in Section 7.1.7.5) may have up to two safety follow-up visits, one after the Treatment Period and one after the Second Course Phase.

7.1.7.4 **Follow-up Visits**

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 (± 7 days) by radiologic imaging to monitor disease status. Every effort should be made to collect information regarding disease status until the start of new anti-neoplastic therapy, disease progression, death, end of the study or if the subject begins retreatment with pembrolizumab as detailed in Section 7.1.7.5. Information regarding post-study anti-neoplastic treatment will be collected if new treatment is initiated.

Subjects who are eligible to receive retreatment with pembrolizumab according to the criteria in Section 7.1.7.5 will move from the follow-up phase to the Second Course Phase when they experience disease progression.

7.1.7.4.1 Survival Follow-up

Once a subject experiences confirmed disease progression or starts a new anti-cancer therapy, the subject moves into the survival follow-up phase and should be contacted by telephone every 12 weeks to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

7.1.7.5 **Second Course Phase (Retreatment Period)**

Subjects who stop pembrolizumab with SD or better may be eligible for up to one year of additional pembrolizumab therapy if they progress after stopping study treatment. This retreatment is termed the Second Course Phase of this study and is only available if the study remains open and the subject meets the following conditions:

- **Either**
    - Stopped initial treatment with pembrolizumab after attaining an investigator-determined confirmed CR according to RECIST 1.1, and
        - Was treated for at least 24 weeks with pembrolizumab before discontinuing therapy
        - Received at least two treatments with pembrolizumab beyond the date when the initial CR was declared

OR

    - Had SD, PR or CR and stopped pembrolizumab treatment after 24 months of study therapy for reasons other than disease progression or intolerability

AND

- Experienced an investigator-determined confirmed radiographic disease progression after stopping their initial treatment with pembrolizumab
- Did not receive any anti-cancer treatment since the last dose of pembrolizumab
- Has a performance status of 0 or 1 on the ECOG Performance Scale
- Demonstrates adequate organ function as detailed in Section 5.1.2
- Male subject should agree to use an adequate method of contraception starting with the first dose of study therapy through 120 days after the last dose of study therapy.
- Does not have a history or current evidence of any condition, therapy, or laboratory abnormality that might 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.

Subjects who restart treatment will be retreated at the same dose and dose interval as when they last received pembrolizumab. Treatment will be administered for up to one additional year.

Visit requirements are outlined in Section 6.0 – Trial Flow Chart.

7.2 Assessing and Recording Adverse Events

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

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

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

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

Progression of the cancer under study is not considered an adverse event.

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

From the time of treatment allocation/randomization through 30 days following cessation of treatment, all adverse events must be reported by the investigator. Such events will be recorded at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in section 7.2.3.1. The investigator will make every attempt to follow all subjects with non-serious adverse events for outcome.

Adverse events will not be collected for subjects during the pre-screening period (for determination of archival tissue status) as long as that subject has not undergone any protocol-specified procedure or intervention. The subject is first required to provide consent to the main study and AEs will be captured according to guidelines for standard AE reporting before blood draw and fresh tumor biopsy.

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

For purposes of this trial, 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. Appropriate supportive treatment should be provided if clinically indicated. In the event of overdose, the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

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

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

All reports of overdose with and without an adverse event must be reported within 24 hours to the Sponsor and within 2 working days hours to Merck Global Safety. (Attn: Worldwide Product Safety; [redacted]220)

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

Although pregnancy and lactation are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject's partner (spontaneously reported to them) that occurs during the trial.

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

Pregnancies and lactations that occur from the time of treatment allocation/randomization through 120 days following cessation of Sponsor's product, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, must be reported by the investigator. All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death,

miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Such events must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX [redacted])

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

7.2.3.1 Serious Adverse Events

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

- Results in death;
- Is life threatening;
- Results in persistent or significant disability/incapacity;
- Results in or prolongs an existing inpatient hospitalization;
- Is a congenital anomaly/birth defect;
- Is an other important medical event

- **Note:** In addition to the above criteria, adverse events meeting either of the below criteria, although not serious per ICH definition, are reportable to the Merck in the same timeframe as SAEs to meet certain local requirements. Therefore, these events are considered serious by Merck for collection purposes.
    - Is a new cancer (that is not a condition of the study);
    - Is associated with an overdose.

Refer to Table 6 for additional details regarding each of the above criteria.

For the time period beginning when the consent form is signed until treatment allocation/randomization, any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study (reference Section 7.2.3.3 for additional details). that occurs to any subject must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study (reference Section 7.2.3.3 for additional details), whether or not related to the Merck product, must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety.

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

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

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

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

7.2.3.2 **Events of Clinical Interest**

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX [redacted]).

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

For the time period beginning at treatment allocation/randomization through 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, any ECI, or follow up to an ECI, whether or not related to Merck product, must be reported within 24 hours to the Sponsor and within 24 hours to Merck Global Safety.

Events of clinical interest for this trial include:

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

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

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

7.2.3.3 **Protocol-Specific Exceptions to Serious Adverse Event Reporting**

Efficacy endpoints as outlined in this section will not be reported to Merck as described in Section 7.2.3 - Immediate Reporting of Adverse Events to the Sponsor and to Merck, unless there is evidence suggesting a causal relationship between the drug and the event. Any such event will be submitted to the Sponsor within 24 hours and to Merck Global Safety within 2 working days either by electronic or paper media.

Specifically, the suspected/actual events covered in this exception include any event that is disease progression of the cancer under study.

The Sponsor will monitor unblinded aggregated efficacy endpoint events and safety data to ensure the safety of the subjects in the trial. Any suspected endpoint which upon review is not progression of the cancer under study will be forwarded to Merck Global Safety as a SAE within 2 working days of determination that the event is not progression of the cancer under study.

Hospitalization related to convenience (e.g. transportation issues etc.) will not be considered a SAE.

7.2.4 Evaluating Adverse Events

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

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

Table 6: Evaluating Adverse Events

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

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

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

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

7.2.5 Sponsor Responsibility for Reporting Adverse Events

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

Reporting to the Data and Safety Monitoring Committee

If a death occurs during the treatment phase of the study or within 30 days after the last administration of the study drug(s) and it is determined to be related either to the study drug(s) or to a study procedure, the Investigator or his/her designee must notify the DSMC Chair (or qualified alternate) within 1 business day of knowledge of the event. The contact may be by phone or e-mail.

Reporting to UCSF Institutional Review Board

The Principal Investigator must report events meeting the UCSF IRB definition of "Unanticipated Problem" (UP) within 5 business days of his/her awareness of the event.

Expedited Reporting to the Food and Drug Administration

If the study is being conducted under an IND, the Sponsor-Investigator is responsible for determining whether or not the suspected adverse reaction meets the criteria for expedited reporting in accordance with Federal Regulations (21 CFR §312.32).

The Investigator must report in an IND safety report any suspected adverse reaction that is both serious and unexpected. The Sponsor-Investigator needs to ensure that the event meets all three definitions:

- Suspected adverse reaction
- Unexpected
- Serious

If the adverse event does not meet all three of the definitions, it should not be submitted as an expedited IND safety report.

The timeline for submitting an IND safety report to FDA is no later than **15 calendar days** after the Investigator determines that the suspected adverse reaction qualifies for reporting (21 CFR 312.32(c)(1)).

Any unexpected fatal or life-threatening suspected adverse reaction will be reported to FDA no later than **7 calendar days** after the Investigator's initial receipt of the information (21 CFR 312.32(c)(2)).

Any relevant additional information that pertains to a previously submitted IND safety report will be submitted to FDA as a Follow-up IND Safety Report without delay, as soon as the information is available (21 CFR 312.32(d)(2)).

8.0 STATISTICAL ANALYSIS PLAN

8.1 Sample Size and Power Calculation

The primary hypothesis of the study is that subjects with defective DNA damage repair have increased radiographic progression free survival (rPFS) compared to subjects with proficient DNA damage repair. With 25 patients in each group, considering 6-month rPFS rate is 10%

for the subjects with proficient DNA damage repair, if 6-month rPFS rate is 45% for the defective DNA damage repair, we have 80% of power to claim that that subjects with defective DNA damage repair have increased radiographic progression free survival (rPFS) compared to subjects with proficient DNA damage repair at one-side alpha of 0.05.

8.2 Statistical Analysis Plan Summary: Primary Objective

8.2.1 Radiographic Progression Free Survival

Radiographic progression free survival (rPFS) is defined as the time from the first day of study treatment with pembrolizumab to the date of documented radiographic tumor progression or death due to any cause, whichever occurs first. Radiographic tumor progression is defined according to the PCWG3 (Scher HI et al., 2016) guidelines.

The point estimate of 6-month rPFS rate and its 95% confidence interval will be obtained for each group, and will be compared by two-sample binomial test. The median rPFS and its 95% confidence interval will be obtained for each study group by Kaplan Meier method. Log rank test will be used to compare rPFS between the two study groups.

8.3 Statistical Analysis Plan Summary: Secondary Objectives

8.3.1 Progression Free Survival

Progression free survival is defined as the time from the first day of study treatment with pembrolizumab to the date of documented tumor progression or death due to any cause, whichever occurs first, as determined by irRC for irPFS and RECIST v1.1 for PFS. Subjects who did not progress or die will be censored on the date of their last evaluable tumor assessment. The point estimation and its 95% confidence interval of 20 weeks and 28 weeks irPFS rate and PFS rate will be obtained by study group and compared between the study groups by two-sample binomial test, separately. Kaplan-Meier method will be used to summarize PFS and irPFS; median irPFS and PFS will be estimated with 95% confidence interval in each study group. Log rank test will be used to compare the irPFS and PFS between the two groups, separately.

8.3.2 PSA Response

The proportion of subjects achieving any PSA response and PSA decline of $\geq$50% from baseline from the time of the first day of study treatment with pembrolizumab will be calculated in both study groups. The duration of PSA response related to treatment duration will be summarized using a radar or spider plot. The point estimate and its 95% confidence interval will be obtained for the proportion of PSA response separately for each study group. Two-sample binomial test will be used to compare the proportion of PSA response between the two study groups.

8.3.3 Safety and Tolerability

All subjects will be evaluated for toxicity from the time of the first treatment with pembrolizumab. Adverse events occurring from the start of treatment until 30 days after the end of treatment will be summarized by maximum toxicity grade for each study group and by strata. The toxicity grade for laboratory data will be calculated using CTCAE v4.0 and the lab data will be summarized according to the subjects' baseline grade and maximum grade for each cycle of therapy. All treatment related adverse events will be graded using NCI CTCAE v4.0.

8.3.4 Time to Progression after Taxane-Based Chemotherapy and Repeat Pembrolizumab

For subjects who undergo taxane-based chemotherapy after progression on pembrolizumab followed by repeat pembrolizumab after chemotherapy, time from the first chemotherapy treatment to disease progression will be estimated in both study groups. Disease progression will be defined by confirmed PSA progression on two consecutive measurements at least 2 weeks apart, or radiographic progression by irRC. The Kaplan-Meier method will be used to estimate the median time to progression with 95% confidence interval by study group. Log rank test will be used to compare the time to progression between the two study groups.

8.4 Statistical Analysis Plan Summary: Exploratory Objectives

8.4.1 Immune Infiltration

Immune cell subsets and localization will be assessed by immunohistochemistry (IHC) in baseline tissue biopsy samples as well as optional tissue biopsy samples at time of progression. Markers will include CD3, CD8 and FoxP3. Differences in immune cell subsets between study groups will be analyzed using Wilcoxon rank-sum test. For available paired samples, changes in immune cell subsets between baseline and progression will be analyzed using Wilcoxon Signed-rank test. In addition, within each study group, Wilcoxon rank-sum test will be used to assess whether there is a relationship between any of the immune cell subsets (both baseline and the change from baseline to progression) and objective response, PSA response, and PFS at 20 and 28 weeks, respectively.

8.4.2 PD-L1 staining

PD-L1 IHC will be performed by Qualtek (CLIA-certified) on baseline and progression biopsy tissues (excluding bone metastases) using Merck's 22C3 antibody. Descriptive statistics will be used to summarize PD-L1 scores between study groups and individuals (when paired samples are available). Moreover, within each study group, Wilcoxon rank-sum test will be used to assess whether there is a relationship between PD-L1 score (both baseline and the change from baseline to progression) with objective response, PSA response, and PFS at 20 and 28 weeks, respectively.

8.4.3 T Cell Receptor (TCR) Repertories

For each subject, blood will be collected at screening, every 3 weeks during treatment, and every 3 months during follow-up. T cell repertoire before, during and after treatment will be assessed by next-generation sequencing. Besides the number of unique clonotypes and read depth, the TCR repertoire diversity will be assessed by Shannon diversity index and clonality. Repertoire overlap will be measured by Baroni-Urbani and Buser index, and changes in clonotypes counts between sequencing experiments will be measured using Morisita's distance. The diversity index will be compared by Wilcoxon rank-sum test between study groups first, then within each study group. Wilcoxon rank-sum test will also be used to assess whether the diversity index is different between responders vs. non-responders (defined by either objective response or PSA response), and between subjects who have progression at 20 and 28 weeks vs. those who have not progressed in each study group.

8.4.4 Mutational Burden

Whole exome sequencing (WES) will be performed in baseline biopsy tissues in a subset of subjects in each study group. The average number of somatic mutations per tumor will be assessed by Wilcoxon rank-sum test between study groups as well as between responders vs. non-responders (defined by either objective response or PSA response), and between subjects who have progression at 20 and 28 weeks vs. those who have not progressed in each study group.

8.4.5 Circulating Immune Cells

For each subject, blood will be collected at screening, every 3 weeks during treatment, and every 3 months during follow-up. Flow cytometry will be performed to assess changes in circulating immune cell subsets with treatment, including effector T cells, regulatory T cells, and myeloid cells. Immune cell quantification will be compared between study groups using Wilcoxon rank-sum test. The Wilcoxon rank-sum test will also be used to assess differences in immune subsets in responders vs. non-responders (defined by either objective response or PSA response), and between subjects who have progression at 20 and 28 weeks vs. those who have not progressed within each study group. Changes in immune cell subsets in individual subjects with treatment will be assessed using Wilcoxon Signed-rank test.

8.4.6 DNA Damage Repair Status Concordance

For subjects who have MSI and FA/BRCA signature testing performed in both baseline biopsy tissue as well as archival primary tissue, the agreement between MSI status and FA/BRCA signature status will be assessed using descriptive statistics.

8.4.7 Clinical Activity in Biomarker Positive Subjects

All subjects enrolled into Group 2 will have DNA damage repair defects by (a) MSI-high only, (b) FA/BRCA signature positive only, or (c) both MSI-high and FA/BRCA signature positive. Chi-square test will be used to examine whether there is relationship between DNA

damage repair defects status with objective response, PSA response rate, and PFS at 20 and 28 weeks.

9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

9.1 Investigational Product

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 in Table 7.

Table 7: Product Descriptions

Product Name & Potency	Dosage Form
Pembrolizumab 50 mg	Lyophilized Powder for Injection
Pembrolizumab 100 mg/ 4mL	Solution for Injection

9.2 Packaging and Labeling Information

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

9.3 Clinical Supplies Disclosure

All subjects in the study will receive pembrolizumab. Drug identity (name, strength) is included in the label text; random code/disclosure envelopes or lists are not provided.

9.4 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.

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

9.5 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 per institutional policy. It is the Investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

10.1 Protection of Human Subjects

10.1.1 Protection from Unnecessary Harm

The Sponsor-Investigator is responsible for protecting all subjects involved in human experimentation. This is accomplished through the IRB mechanism and the process of informed consent. The IRB reviews all proposed studies involving human experimentation and ensures that the subject's rights and welfare are protected and that the potential benefits and/or the importance of the knowledge to be gained outweigh the risks to the individual. The IRB also reviews the informed consent document associated with each study in order to ensure that the consent document accurately and clearly communicates the nature of the research to be done and its associated risks and benefits.

10.1.2 Protection of Privacy

Patients will be informed of the extent to which their confidential health information generated from this study may be used for research purposes. Following this discussion, they will be asked to sign the HIPAA form and informed consent documents. The original signed document will become part of the patient's medical records, and each patient will receive a copy of the signed document. The use and disclosure of protected health information will be limited to the individuals described in the informed consent document.

10.2 Compliance with Financial Disclosure Requirements

For all Principal Investigators and Sub-Investigators listed on the FDA 1572, Financial Disclosure Forms, CVs, MD Licenses, Drug Enforcement Agency (DEA) Licenses, and Staff Training Documents (i.e. Collaborative Institute Training Initiative (CITI), etc.) will be required.

10.3 Compliance with Law, Audit and Debarment

The UCSF Helen Diller Family Comprehensive Cancer Center DSMC will be the monitoring entity for this study. The UCSF DSMC will monitor the study in accordance with the NCI-approved Data and Safety Monitoring Plan (DSMP). The DSMC will routinely review all adverse events and suspected adverse reactions considered "serious". The DSMC will audit study-related activities to ensure that the study is conducted in accordance with the protocol, local standard operating procedures, FDA regulations, and Good Clinical Practice (GCP). Significant results of the DSMC audit will be communicated to the IRB and the appropriate regulatory authorities at the time of continuing review, or in an expedited fashion, as applicable. See Appendix 11.5 Data and Safety Monitoring Plan for a Phase 2 or 3 Institutional Study, for additional information.

10.4 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the Sponsor of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to the Clinical Trials Data Bank, http://www.clinicaltrials.gov. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information.

10.5 Study Management

10.5.1 Pre-Study Documentation

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki as stated in 21 CFR §312.120(c)(4); consistent with GCP and all applicable regulatory requirements.

Before initiating this trial, the Investigator will have written and dated approval from the Institutional Review Board for the protocol, written informed consent form, subject recruitment materials, and any other written information to be provided to subjects before any protocol related procedures are performed on any subjects.

The clinical investigation will not begin until either FDA has determined that the study under the Investigational Drug Application (IND) is allowed to proceed or the Investigator has received a letter from FDA stating that the study is exempt from IND requirements.

The Investigator must comply with the applicable regulations in Title 21 of the Code of Federal Regulations (21 CFR §50, §54, and §312), GCP/ICH guidelines, and all applicable regulatory requirements. The IRB must comply with the regulations in 21 CFR §56 and applicable regulatory requirements.

10.5.2 Institutional Review Board Approval

The protocol, the proposed informed consent form, and all forms of participant information related to the study (e.g. advertisements used to recruit participants) will be reviewed and approved by the UCSF IRB (UCSF Institutional Review Board). Prior to obtaining IRB approval, the protocol must be approved by the Helen Diller Family Comprehensive Cancer Center Site Committee and by the Protocol Review Committee (PRC). The initial protocol and all protocol amendments must be approved by the IRB prior to implementation.

10.5.3 Informed Consent

All participants must be provided a consent form describing the study with sufficient information for each participant to make an informed decision regarding their participation. Participants must sign the IRB-approved informed consent form prior to participation in any study specific procedure. The participant must receive a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file.

10.5.4 Changes in the Protocol

Once the protocol has been approved by the UCSF IRB, any changes to the protocol must be documented in the form of an amendment. The amendment must be signed by the Investigator and approved by PRC and the IRB prior to implementation.

If it becomes necessary to alter the protocol to eliminate an immediate hazard to patients, an amendment may be implemented prior to IRB approval. In this circumstance, however, the Investigator must then notify the IRB in writing within five (5) working days after implementation.

10.5.5 Handling and Documentation of Clinical Supplies

The UCSF Principal Investigator will maintain complete records showing the receipt, dispensation, return, or other disposition of all investigational drugs. The date, quantity and batch or code number of the drug, and the identification of patients to whom study drug has been dispensed by patient number and initials will be included. The sponsor-investigator will maintain written records of any disposition of the study drug.

The Principal Investigator shall not make the investigational drug available to any individuals other than to qualified study patients. Furthermore, the Principal Investigator will not allow the investigational drug to be used in any manner other than that specified in this protocol.

10.5.6 Case Report Forms (CRFs)

The Principal Investigator and/or his/her designee, will prepare and maintain adequate and accurate participant case histories with observations and data pertinent to the study. Study specific Case Report Forms (CRFs) will document safety and treatment outcomes for safety monitoring and data analysis. All study data will be entered into OnCore® via standardized CRFs in accordance with the CTMS study calendar, using single data entry with a secure access account. The Clinical Research Coordinator (CRC) will complete the CRFs as soon as possible upon completion of the study visit; the Investigator will review and approve the completed CRFs.

The information collected on CRFs shall be identical to that appearing in original source documents. Source documents will be found in the patient's medical records maintained by UCSF personnel. All source documentation should be kept in separate research folders for each patient.

In accordance with federal regulations, the Investigator is responsible for the accuracy and authenticity of all clinical and laboratory data entered onto CRFs. The PI will approve all completed CRFs to attest that the information contained on the CRFs is true and accurate.

All source documentation and CTMS data will be available for review/monitoring by the UCSF DSMC and regulatory agencies.

The Principal Investigator will be responsible for ensuring the accurate capture of study data. At study completion, when the CRFs have been declared to be complete and accurate, the database will be locked. Any changes to the data entered into the CRFs after that time can only be made by joint written agreement among the Principal Investigator, the Trial Statistician, and the Protocol Project Manager.

10.5.7 Oversight and Monitoring Plan

See Section 10.4. The UCSF Helen Diller Family Comprehensive Cancer Center DSMC will be the monitoring entity for this study. The UCSF DSMC will monitor the study in accordance with the NCI-approved Data and Safety Monitoring Plan (DSMP). The DSMC will routinely review all adverse events and suspected adverse reactions considered "serious". The DSMC will audit study-related activities to ensure that the study is conducted in accordance with the protocol, local standard operating procedures, FDA regulations, and Good Clinical Practice (GCP). Significant results of the DSMC audit will be communicated to the IRB and the appropriate regulatory authorities at the time of continuing review, or in an expedited fashion, as applicable. See Appendix 11.6 Data and Safety Monitoring Plan for a Phase 2 or 3 Institutional Study, for additional information.

11.0 APPENDICES

11.1 Performance Status Criteria

ECOG PERFORMANCE STATUS	KARNOFSKY PERFORMANCE STATUS
0—Fully active, able to carry on all pre-disease performance without restriction	100—Normal, no complaints; no evidence of disease 90—Able to carry on normal activity; minor signs or symptoms of disease
1—Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work	80—Normal activity with effort, some signs or symptoms of disease 70—Cares for self but unable to carry on normal activity or to do active work
2—Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours	60—Requires occasional assistance but is able to care for most of personal needs 50—Requires considerable assistance and frequent medical care
3—Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours	40—Disabled; requires special care and assistance 30—Severely disabled; hospitalization is indicated although death not imminent
4—Completely disabled; cannot carry on any selfcare; totally confined to bed or chair	20—Very ill; hospitalization and active supportive care necessary 10—Moribund
5—Dead	0—Dead

*Karnofsky D, Burchenal J, The clinical evaluation of chemotherapeutic agents in cancer. In: MacLeod C, ed. Evaluation of Chemotherapeutic Agents. New York, NY: Columbia University Press; 1949:191–205.
**Zubrod C, et al. Appraisal of methods for the study of chemotherapy in man: Comparative therapeutic trial of nitrogen mustard and thiophosphoramide. *Journal of Chronic Diseases*; 1960:11:7-33.

11.2 Common Terminology Criteria for Adverse Events V4.0 (CTCAE)

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

11.3 Prostate Cancer Clinical Trials Working Group 3 (PCWG3)

The Prostate Cancer Clinical Trials Working Group 3 (PCWG3) guidelines* for assessment of radiographic progression for primary outcome measure.

As published in the Journal of Clinical Oncology

Scher HI, Morris MJ, Stadler WM, Higano C, Basch E, Fizazi K, Antonarakis ES, Beer TM, Carducci MA, Chi KN, Corn PG. Trial design and objectives for castration-resistant prostate cancer: updated recommendations from the Prostate Cancer Clinical Trials Working Group 3. Journal of Clinical Oncology. 2016 Apr 20;34(12):1402.

11.4 Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 Criteria for Evaluating Response in Solid Tumors

RECIST version 1.1* will be used in this study for assessment of tumor progression for measurable disease. While either CT or MRI may be utilized, as per RECIST 1.1, CT is the preferred imaging technique in this study.

* As published in European Journal of Cancer:

E.A. Eisenhauer, P. Therasse, J. Bogaerts, L.H. Schwartz, D. Sargent, R. Ford, J. Dancey, S. Arbuck, S. Gwyther, M. Mooney, L. Rubinstein, L. Shankar, L. Dodd, R. Kaplan, D. Lacombe, J. Verweij. New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1). Eur J Cancer. 2009 Jan;45(2):228-47.

11.5 Immune-Related Response Criteria (irRC) for Evaluation of Immune Therapy Activity in Solid Tumors

Immune-related response criteria (irRC)* will also be used in this study for assessment of tumor progression for measurable disease.

* As published in Clinical Cancer Research:

J.D. Wolchok, A. Hoos, S. O'Day, J.S. Weber, O. Hamid, C. Lebbe, M. Maio, M. Binder, O. Bohnsack, G Nichol, R Humphrey, S.F. Hodi . Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. Clin Cancer Res. 2009 Dec;15(23): 7412-7420.

11.6 Data and Safety Monitoring Plan for a Phase 2 or 3 Institutional Study

1. Oversight and Monitoring Plan

The UCSF Helen Diller Family Comprehensive Cancer Center (HDFCCC) Data and Safety Monitoring Committee (DSMC) is responsible for monitoring data quality and subject safety for all HDFCCC institutional clinical studies. A summary of DSMC activities for this study includes:

- Review of patient data.
- Review of serious adverse events.
- Auditing every six months (depending on study accrual).
- Minimum of a yearly regulatory audit.

2. Monitoring and Reporting Guidelines

Investigators will conduct continuous review of data and patient safety and discuss each patient's treatment at monthly site committee meetings. These discussions are documented in the site committee meeting minutes. The discussion will include the number of patients, significant toxicities in accordance with the protocol, and observed responses.

All institutional Phase II and III studies are designated with a moderate risk assessment (see Appendix H). The data is audited twice per year with twenty percent of the patients monitored (or at least three patients if the calculated value is less than three).

3. Review and Oversight Requirements

3.1 Adverse Event Monitoring

All Grade 3-5 Adverse Events (AEs), whether or not considered to be expected or unexpected and whether or not considered to be associated with the use of the study drug, will be entered into OnCore®, UCSF's Clinical Trial Management System.

Adverse Events are graded according to the Common Terminology Criteria for Adverse Events (CTCAE) (version 4.03) as developed and revised by the Common Therapy Evaluation Program (CTEP) of the National Cancer Institute. Adverse events are further given an assignment of attribution or relationship to treatment or medical procedure.

Attribution categories are:

- **Definite** – The adverse event is clearly related to the investigational agent(s) or medical procedure.
- **Probable** – The adverse event is likely related to the investigational agent(s) or medical procedure.
- **Possible** – The adverse event may be related to the investigational agent(s) or medical procedure.
- **Unlikely** – The adverse event is doubtfully related to the investigational agent(s) or medical procedure.
- **Unrelated** – the adverse event is clearly not related to the investigational agent(s) or medical procedure.

All Grade 3-5 adverse events entered into OnCore® will be reviewed on a monthly basis at the Site Committee meetings. The Site Committee will review and discuss the selected toxicity, the toxicity grade, and the attribution of relationship of the adverse event to the administration of the study drug(s).

3.2 Serious Adverse Event Reporting

By definition, an adverse event is defined as a serious adverse event (SAE) according to the following criteria:

- Death.
- Life-threatening (i.e. results in an immediate risk of death).
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Permanent or significant disability/incapacity
- Gives rise to a congenital anomaly/birth defect, or cancer, or any experience that suggests a significant hazard, contraindication, side effect, or precaution that may require medical or surgical intervention to prevent one of the outcomes listed above.
- Event occurring in a gene therapy study.
- Event that changes the risk/benefit ratio of a study.
- Any other event the Principal Investigator judges to be serious or which would suggest a significant hazard, contraindication, side effect, or precaution.

Serious Adverse Event reporting will be in accordance with the UCSF IRB Regulations and Code of Federal Regulation Title 21 Part 312.32. The SAE will be reported on a Med Watch form.

UCSF IRB website for guidance in reporting serious adverse events:
https://irb.ucsf.edu/adverse-event

FDA website for guidance in reporting serious adverse events:
www.fda.gov/Safety/MedWatch/HowToReport/default.htm

Med Watch forms and information:
www.fda.gov/medwatch/getforms.htm

All serious adverse events are entered into OnCore®, as well as submitted to the IRB (per IRB guidelines) via iMedRIS®. The SAEs are reviewed and monitored by the Data and Safety Monitoring Committee on an ongoing basis and discussed at DSMC meetings, which take place every six weeks. The date the SAE is sent to all required reporting agencies will be documented in OnCore®.

If the SAE involves a subject death, and is determined to be possibly, probably or definitely related to the investigational drug or any research related procedure, the event must be reported to the DSMC Chair or Vice Chair within 1 business day.
The reporting procedure is by communication via phone or in person with written documentation of the one-on-one communication via e-mail, with a copy of the e-mail to the DSMC Manager.

3.3 Review of Adverse Event Rates

If an increase in the frequency of Grade 3 or 4 adverse events (above the rate reported in the Investigator Brochure or package insert) is noted in the study, the Principal Investigator will notify the DSMC at the time the increased rate is identified. The report will indicate if the incidence of adverse events observed in the study is above the range stated in the Investigator Brochure or package insert.
If at any time the Investigator stops enrollment or stops the study due to safety issues, the DSMC Chair and DSMC Manager must be notified within 1 business day via e-mail and the IRB must be notified within 10 business days via an iRIS Reporting Form.

Data and Safety Monitoring Committee Contacts:

Thierry Jahan, MD
[redacted]
UCSFHDFCCCC
San Francisco, CA 94158

DSMC Monitors
[redacted]
UCSF Helen Diller Family
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12.0 ABBREVIATIONS

ADT	androgen deprivation therapy
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
ATM	ataxia-telangiectasia mutated
BUN	blood urea nitrogen
CBC	complete blood cell (count)
CR	complete response
CRC	Clinical Research Coordinator
CRF	case report form
CRPC	castrate-resistant prostate cancer
CT	computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
CTMS	Clinical Trial Management System
DDRD	DNA damage response deficiency
DEA	Drug Enforcement Agency
DSMC	Data and Safety Monitoring Committee
DSMP	Data and Safety Monitoring Plan
ECI	Events of Clinical Interest
ECOG	Eastern Cooperative Oncology Group
FA	Fanconi anemia
FDA	Food and Drug Administration
FT3	free triiodothyronine
FT4	free thyroxine
GCP	Good Clinical Practice
GNRH	gonadotropin-releasing hormone
HBsAg	Hepatitis B surface antigen
HCV	hepatitis C virus
HDFCCC	Helen Diller Family Comprehensive Cancer Center
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus

ICH	International Conference on Harmonization
IDO1	Indoleamine 2,3-Dioxygenase 1
IHC	immunohistochemistry
IND	investigational new drug application
IP	investigational product
IRB	Institutional Review Board
irPFS	immune-related progression free survival
irRC	immune-related response criteria
IV	intravenous
LDH	lactate dehydrogenase
mAb	monoclonal antibody
mCRPC	metastatic castrate resistant prostate cancer
MMR	mismatch repair
MRI	magnetic resonance imaging
MSAS	minimum sufficient adjustment sets
MSI	microsatellite instability
MSS	microsatellite stable
MTD	maximum tolerated dose
Na-F	sodium fluoride
NCI	National Cancer Institute
NSCLC	non-small cell lung cancer
OCT	over-the-counter
PAP	prostatic acid phosphatase
PCWG3	Prostate Cancer Clinical Trials Working Group 3
PD-1	programmed death 1 (PD-1)
PD-L1	programmed death-ligand 1 (PD-L1)
PD-L2	programmed death-ligand 2 (PD-L2)
PET	positron emission tomography
PFS	progression free survival
PK	pharmacokinetics
PO	*Per os* (by mouth, orally)
PRC	Protocol Review Committee (UCSF)
PSA	prostate specific antigen
Q2W	every 2 weeks
Q3W	every 3 weeks
RBC	red blood cell (count)
RECIST	Response Evaluation Criteria in Solid Tumors

rPFS	Radiographic progression-free survival
Rx	treatment
SD	stable disease
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
TILs	tumor-infiltrating lymphocytes
ULN	upper limit of normal
TCR	T cell receptor
Treg	regulatory T cells
TSH	thyroid-stimulating hormone
WBC	white blood cell (count)
WES	whole exome sequencing

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