SPONSOR: Oregon Health & Science University

TITLE: Addition of Pembrolizumab Upon Progression on Enzalutamide in men with mCRPC

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1.0 TRIAL SUMMARY

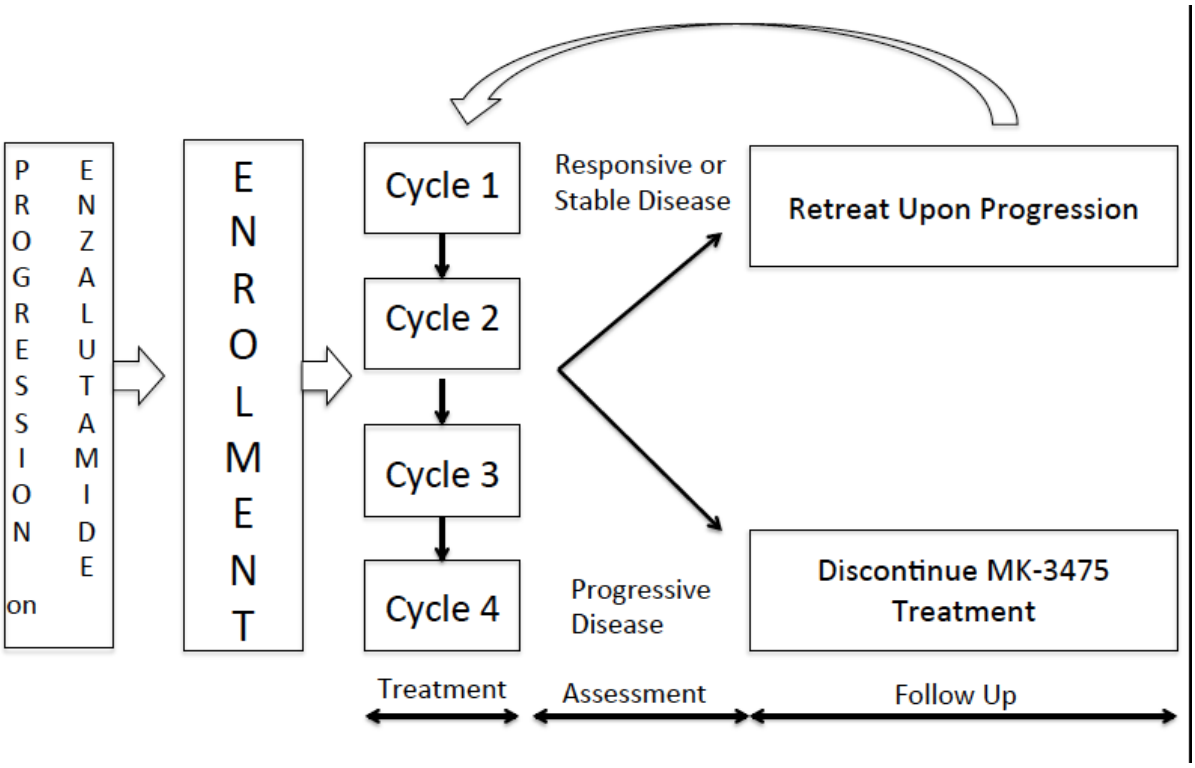
Abbreviated Title	**Pembrolizumab plus enzalutamide in progression with enzalutamide alone**
Trial Phase	II
Clinical Indication	Castration-resistant prostate cancer, progressing on enzalutamide
Trial Type	Interventional, single arm
Type of control	Historical
Route of administration	Intravenous Pembrolizumab
Trial Blinding	N/A
Treatment Groups	Single-arm Pembrolizumab + enzalutamide (standard of care)
Number of trial subjects	58
Estimated duration of trial	5 years (2.5 years of enrolment, 2.5 years of follow up)
Duration of Participation	2 years

2.0 TRIAL DESIGN

2.1 Trial Design

Single-arm phase II study of adding pembrolizumab in men with metastatic, castration resistant prostate cancer progressing on enzalutamide.

2.2 Trial Diagram



3.0 OBJECTIVES & HYPOTHESES

3.1 Primary Objectives & Hypotheses

Objectives: Measure the anti-cancer activity of pembrolizumab in men with metastatic, castration resistant prostate cancer. A response to treatment will be defined by a PSA decrease of at least 50%. Examine the safety of the combination of pembrolizumab with enzalutamide by looking at adverse events by the CTCAE v.4.

Hypothesis: Immunological therapy with pembrolizumab combined with a second generation receptor antagonist will be safe and lead to PSA responses in men with mCRPC beginning to progress on enzalutamide.

3.2 Secondary Objectives, Exploratory Objectives, & Hypotheses

Secondary Objectives:
(1) To investigate immunological and genetic parameters to evaluate for possible markers and functional changes that are predictive of a clinical response or linked to response or resistance to PD-1 inhibition. Exploratory analyses will include:

- Immunohistochemistry for total CD45+ cells (leukocytes), lymphocytes (CD8+, CD4+, and B cells), and macrophages in prostate tissue at diagnosis (if original biopsy is available) and pre-treatment
- Immunohistochemisty for PD-1, PD-L1 and PD-L2 in prostate tissue at diagnosis (if original biopsy is available) and pre-treatment
- DNA sequencing

(1) To collect circulating tumor cells (CTCs) and determine the degree to which tumor characteristics are shared by the CTCs.
(2) Changes in T cell numbers, activation, and phenotype as measured in whole blood at diagnosis and throughout therapy

- T effector/memory panel (CD45, CD3, CD8, CCR7, CD45RA,CD45RO, CD69, CD44, CD62L)
- T regulatory panel (CD45, CD3, CD4, FoxP3, CD25, CD127, CD69, CD44)
- T help panel (CD45, CD3, CD4, CD45RA, CD45RO, CD69, CD44, CD62L)
- Cytokine propensity of the above T cell subsets (IFN-γ, IL-2, IL-4, IL-12, IL-13, IL-10, IL-18, TNF-α, TGF-β, IL-17)

(3) Systemic inflammatory markers: Serum IL-8, IL-6, IL-1, TNF and TGF-beta
(4) Objective disease response by radiographs
(5) PSA progression free survival
(6) Overall survival
(7) Microbiome and correlation with response

Exploratory Objectives:

(1) Additional genetic (DNA, RNA) and protein analyses will be conducted to further evaluate immunotherapy and profile/characterize disease

Hypotheses: Clinical outcomes will correlate with T cell activation/phenotype, the presence of CD8+ lymphocytes in the prostate cancer biopsy (metastatic); circulating tumor cells will share tumor characteristics and can possibly be used as a surrogate to tissue biopsy in future studies; and, increases in systemic inflammatory markers will be inversely related to response. Immunological therapy with pembrolizumab combined with a powerful androgen receptor will lead to PSA progression free survival prolongation in men with mCRPC beginning to progress on enzalutamide.

4.0 BACKGROUND & RATIONALE

4.1 Background

4.1.1 Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades (1). Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various

malignancies (2-6). 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) (7, 8). The structure of murine PD-1 has been resolved (9). 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 (7, 10-12). 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 (13, 14). 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 (15, 16). Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells (17). 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 (13, 18-20). 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 (13). 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) (21). 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 (previously known as SCH 900475 and MK-3475) 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.

Our 38th subject just completed four cycles of pembrolizumab. We have seen seven robust responses so far. The degree of response is surprising, and we do not currently understand the

mechanism. We are expanding enrolment to an additional 30 patients with enriched correlative work to help us understand which patients respond to this therapy.

4.1.2 Preclinical and Clinical Trial Data

Refer to the Investigator's Brochure (IB) 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) is prostate cancer that no longer responds to castration alone, either surgically or chemically, and consequently is the terminal disease state in prostate cancer. There are several agents that can prolong survival after development of mCRPC, but none are curative. It is unclear how best to treat patients who are progressing on the androgen receptor antagonist enzalutamide. Patients who progress on enzalutamide do not respond as well to abiraterone as those who have not been exposed to enzalutamide(22) (23). The FDA approved immunotherapy, sipuleucel-T, has very little effect on tumor size and is only used in a select group of patients with very slow growing tumors.(24) Chemotherapy with docetaxel is another option for these patients, but its use is often delayed in order to avoid the associated toxicity.(25, 26) Additionally, there are data suggesting that the combination of enzalutamide with immunotherapy may be effective in this population.(27)

4.2.2 Rationale for Dose Selection/Regimen/Modification

An open-label Phase I trial (Protocol 001) is being conducted to evaluate the safety and clinical activity of single agent pembrolizumab. 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 pembrolizumab 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 Maximum Tolerated Dose (MTD) has been identified to date. Recent data from other clinical studies within the pembrolizumab program has shown that a lower dose of pembrolizumab and a less frequent schedule may be sufficient for target engagement and clinical activity.

PK data analysis of pembrolizumab 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 pembrolizumab 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. Pembrolizumab 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 pembrolizumab 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.

Based on the studies described above, we will be using pembrolizumab 200 mg (fixed dose) IV every 3 weeks.

4.2.3 Rationale for Endpoints

4.2.3.1 Efficacy Endpoints

Patients with PSA progression on treatment are extremely unlikely to have a PSA response without a change in therapy. PSA changes, while not always correlated with survival, provide a readily measurable means of assessing prostate cancer response or progression. We will use this endpoint as our primary outcome. However, we will use radiographic progression when determining a subject's suitability to continue on treatment. Furthermore, since the benefits of immunotherapy can take months to become apparent, we will not make treatment decisions within the first 12 weeks.

4.2.3.2 Biomarker Research

First, T cell number can indicate response to immunotherapy – at least its pharmacokinetic effect.(28) We will look at T cell subtypes and correlate with clinical response. Second, we are collecting tissue from baseline diagnosis (archival tissue) and from metastatic tumor biopsy. There are data in melanoma and breast cancer correlating the immunophenotype to treatment response (29, 30). There are not yet many data in prostate cancer, and this trial seeks to increase our understanding of it. Third, we will look at inflammatory markers to see how they correspond with response.

Banking of Specimens for Potential Future Research. Specimens collected and any leftover serum/plasma will be banked for future research under the "Master Protocol for Cancer Research Specimen Bank and Database" (OHSU IRB 2816), and will be used to search for biomarkers of response and resistance to therapy. Future research may include genetic research.

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial: Metastatic, castration resistant prostate cancer progressing on enzalutamide after initial response to enzalutamide.

5.1.2 Subject Inclusion Criteria

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

1. Histologically or cytologically confirmed adenocarcinoma of the prostate without pure small cell carcinoma. Patients without histologically confirmed adenocarcinoma may be eligible if both the treating physician and the study PI agree that the patient's history is unambiguously indicative of advanced adenocarcinoma.

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

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

4. Have metastatic disease.

5. Have permission to access tissue from an archival tissue sample. (Absence of archival tissue will not preclude trial participation.)

6. Has a metastatic deposit that can be biopsied.

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

8. Demonstrate adequate organ function as defined in Table 1, all screening labs 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
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 **OR**

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

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

10. Have a PSA or radiographic progression on enzalutamide. PSA progression is defined as two consecutive increases in PSA with the second level obtained at least 3 weeks after the first, and the second level of at least 0.5 ng/mL. Soft tissue disease progression defined by RECIST 1.1 criteria or ≥ 2 new lesions on bone scan.

11. Have had either surgical castration OR be on LHRH agonist or antagonist therapy with serum testosterone <50 ng/dl AND agree to stay on LHRH agonist or antagonist therapy during the study.

5.1.3 Subject Exclusion Criteria

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

1. Is currently participating in or has participated in a study of an investigational agent or using an investigational device within 4 weeks of the first dose of treatment.

2. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.

3. Has had a prior monoclonal antibody 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. **Denosumab is a prohibited medication** on study and for 4 weeks prior to day 1.

4. Has had chemotherapy for castration-resistant disease. Chemotherapy for castration-sensitive disease is permitted.

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

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

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

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

7. Has known brain metastases and/or carcinomatous meningitis.

8. Has a history of seizure

9. Has allergy to enzalutamide

10. Has an active automimmune disease requiring systemic treatment within the past 3 months or a documented history of clinically severe autoimmune disease, or a syndrome that requires systemic steroids or immunosuppressive agents. A severe autoimmune disease is one that requires a significant medical intervention such as hospitalization. Subjects with vitiligo or resolved childhood asthma/atopy would be an exception to this rule. Subjects that require intermittent use of bronchodilators or local steroid injections would not be excluded from the study. Subjects with hypothyroidism stable on hormone replacement or Sjorgen's syndrome will not be excluded from the study.

11. Has a history of (non-infectious) pneumonitis that required steroids or current pneumonitis. Has an active infection requiring systemic therapy.

12. 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.

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

14. Has received prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody (including ipilimumab or

any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways). Previous treatment with sipuleucel-T is permitted.

15. Has plans to receive cytotoxic chemotherapy, immune checkpoint inhibitors (eg CTLA-4 blockade), sipuleucel-T, radiopharmaceuticals, abiraterone or other experiemental therapy during this study period.

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

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

18. Has received a live vaccine within 30 days prior to the first dose of trial treatment.

19. Has rapid progression of visceral disease and, thus is a candidate for docetaxel. This determination will be at the discretion of the treating physician.

5.2 Trial Treatments

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

Table 2 Trial Treatment

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period	Use
Pembrolizumab	200 mg	Every 3 weeks	IV infusion	Four doses	Experimental
Enzalutamide	80-160 mg	Daily	By mouth	Throughout study	Standard of Care
Then, if progressing after initial response or stability (see section 7.1.2.11),					
Pembrolizumab	200 mg	Every 3 weeks	IV infusion	Four doses	Experimental
Enzalutamide	80-160 mg	Daily	By mouth	Throughout study	Standard of Care
The pembrolizumab dosing interval may be increased due to toxicity as described in Section 5.2.1.2.					

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. We will use pembrolizumab 200 mg (fixed dose) IV every 3 weeks.

Details on the dose calculation, preparation and administration are provided in the Pharmacy Manual.

5.2.1.2 Dose Modification

Pembrolizumab will be withheld for drug-related Grade 4 hematologic toxicities, non-hematological toxicity ≥ Grade 3 including laboratory abnormalities, and severe or life-threatening AEs as per Table 3 below.

Table 3: Dose modification guidelines for non-immune related drug-related adverse events.

Toxicity	Grade	Hold Treatment (Y/N)	Timing for restarting treatment	Dose/Schedule for restarting treatment	Discontinue Subject (after consultation with Coordinating Center, OHSU)
Hematological Toxicity	1, 2	No	N/A	N/A	N/A
	3* *Excluding Grade 3 neutropenia, anemia, and thrombocytopenia	Yes	Toxicity resolves to Grade 0-1 or baseline	May increase the dosing interval by 1 week	Toxicity does not resolve within 12 weeks of last infusion *Permanent discontinuation should be considered for any severe or life-threatening event*
	4	Yes	Toxicity resolves to Grade 0-1 or baseline	May increase the dosing interval by 1 week	
Non-hematological toxicity Note: Exception to be treated similar to grade 1 toxicity • Grade 2 alopecia • Grade 2 fatigue For additional information regarding Adverse Events with	1	No	N/A	N/A	N/A
	2	Consider withholding for persistent symptoms	Toxicity resolves to Grade 0-1 or baseline	*Clinical AE resolves within 4 weeks*: Same dose and schedule (reference Section 5.6.1.2 for recommendations regarding pneumonitis)	Toxicity does not resolve within 12 weeks of last infusion

Toxicity	Grade	Hold Treatment (Y/N)	Timing for restarting treatment	Dose/Schedule for restarting treatment	Discontinue Subject (after consultation with Coordinating Center, OHSU)
a potential Immune-Etiology reference Section 5.6.1.1.				*Clinical AE does not resolve within 4 weeks:* May increase the dosing interval by 1 week for each occurrence	
	3, 4	Yes	Toxicity resolves to Grade 0-1 or baseline	May increase the dosing interval by 1 week for each occurrence	Toxicity does not resolve within 12 weeks of last infusion *Permanent discontinuation should be considered for any severe or life-threatening event*

In case toxicity does not resolve to Grade 0-1 within 12 weeks after last infusion, trial treatment should be discontinued after consultation with Dr. Graff at OHSU. With investigator and Dr. Graff agreement, subjects with a laboratory adverse event still at Grade 2 after 12 weeks may continue treatment in the trial only if asymptomatic and controlled. For information on the management of adverse events, see Section 5.6.1.

Subjects who experience a recurrence of the same severe or life-threatening event at the same grade or greater with re-challenge of pembrolizumab should be discontinued from trial treatment.

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 will be administered as a 30 minute IV infusion (treatment cycle intervals may be increased due to toxicity as described in Section 5.2.1.2). Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min).

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

5.2.3 Trial Blinding/Masking

This is an open-label trial; therefore, the investigator and subject will know the treatment administered.

5.3 Randomization or Treatment Allocation

This is not a randomized trial. All patients will receive treatment.

5.4 Stratification

There will not be up-front stratification.

5.5 Concomitant Medications/Vaccinations (allowed & prohibited)

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

External beam radiation therapy is permitted on this study. Its use should be disclosed and described (dose, number of areas, number of treatments, treatment dates and response) as a Concomitant Therapy in clinical report forms. There are no data regarding the simultaneous use of radiation and pembrolizumab. Therefore, if radiation is needed, the pembrolizumab should be held one week prior to radiation and for 2 weeks after radiation therapy.

Subjects eligible for this study are progressing on enzalutamide and must continue the enzalutamide while on this study. However, enzalutamide may be held for adverse events thought to be related to enzalutamide. If a subject is off of enzalutamide for longer than 30 consecutive days, either directly prior to starting the study or after enrollment, the principal investigator needs to be alerted.

5.5.1 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.

As noted above, external beam radiation is permitted, and enzalutamide should be continued. Radium-223, strontium and samarium are prohibited.

5.5.2 Prohibited Concomitant Medications

Subjects are prohibited from receiving the following therapies during the Screening and Treatment Phase (including retreatment) of this trial:

- Anti-cancer systemic chemotherapy, hormone therapy or biological therapy
- Immunotherapy not specified in this protocol
- Radiopharmaceuticals such as Radium-223, strontium, and samarium
- Investigational agents other than pembrolizumab
- Live vaccines within 30 days prior to the first dose of trial treatment and during active treatment. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however intranasal influenza vaccines (e.g. Flu-Mist®) are live attenuated vaccines, and are not allowed.
- Glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.
- Agents that can affect PSA, other than LHRH-agonists and enzalutamide. Examples of these agents include bicalutamide, flutamide, nilutamide, abiraterone, prednisone, and herbal agents such as PC-SPES and saw palmetto.
- Denosumab (also known as Prolia and Xgeva) is prohibited because it can be immunosuppressive.

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 Monitoring Phase.

5.6 Rescue Medications & Supportive Care

5.6.1 Supportive Care Guidelines

Adverse events experienced on study may be related to the study agent (pembrolizumab), enzalutamide, cancer itself, or another etiology. If the side effect is felt related to the pembrolizumab, please follow the recommended supportive care guidelines below. If the side effect is attributable to something other than pembrolizumab, these guidelines may not apply, and a more appropriate treatment may be needed. Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator including but not limited to the items outlined below:

- Diarrhea: 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). In symptomatic subjects, infectious etiologies should be ruled out, and if symptoms are persistent and/or severe, endoscopic evaluation should be considered.

    - In subjects with severe enterocolitis (Grade >2), pembrolizumab will be permanently discontinued and treatment with systemic corticosteroids should be initiated at a dose of 1 to 2 mg/kg/day of prednisone or equivalent. When symptoms improve to Grade 1 or less, corticosteroid taper should be started and continued over at least 1 month.

    - In subjects with moderate enterocolitis (Grade 2), pembrolizumab should be withheld and anti-diarrheal treatment should be started. If symptoms are persistent for more than one week, systemic corticosteroids should be initiated (e.g., 0.5 mg/kg/day of prednisone or equivalent). When symptoms improve to Grade 1 or less, corticosteroid taper should be started and continued over at least 1 month. Regarding guidelines for continuing treatment with pembrolizumab, see Section 5.2.

    - All subjects who experience diarrhea 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.

- Nausea/vomiting: Nausea and vomiting should be treated aggressively, and consideration should be given in subsequent cycles to the administration of prophylactic antiemetic therapy according to standard institutional practice. Subjects should be strongly encouraged to maintain liberal oral fluid intake.

- Anti-infectives: Subjects with a documented infectious complication should receive oral or IV antibiotics or other anti-infective agents as considered appropriate by the treating investigator for a given infectious condition, according to standard institutional practice.

- Immune-related adverse events: Please see Section 5.6.1.1 below and Section 12.6 regarding diagnosis and management of adverse experiences of a potential immunologic etiology.

- Management of Infusion Reactions: Acute infusion reactions (which can include cytokine release syndrome, angioedema, or anaphylaxis) are different from allergic/hypersensitive reactions, although some of the manifestations are common to both AEs. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Signs/symptoms may include: Allergic reaction/hypersensitivity (including drug fever); Arthralgia (joint pain); Bronchospasm; Cough; Dizziness; Dyspnea (shortness of breath); Fatigue (asthenia, lethargy, malaise); Headache; Hypertension; Hypotension; Myalgia (muscle pain); Nausea; Pruritis/itching; Rash/desquamation; Rigors/chills; Sweating (diaphoresis); Tachycardia; Tumor pain (onset or exacerbation of tumor pain due to treatment); Urticaria (hives, welts, wheals); Vomiting.

Table 4 below shows treatment guidelines for subjects who experience an infusion reaction associated with administration of pembrolizumab.

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	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine).

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
	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.**	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. For Further information, please refer to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE) at http://ctep.cancer.gov		

5.6.1.1 Supportive Care Guidelines for Immune-related Adverse Events (irAEs)

Events of clinical interest of a potential immunologic etiology (irECIs) may be defined as an adverse event of unknown etiology, associated with drug exposure and is consistent with an immune phenomenon. irAEs may be predicted based on the nature of the pembrolizumab compound, its mechanism of action, and reported experience with immunotherapies that have a similar mechanism of action. Special attention should be paid to AEs that may be suggestive of potential irAEs. An irAE can occur shortly after the first dose or several months after the last dose of treatment.

If an irAE is suspected, efforts should be made to rule out neoplastic, infectious, metabolic, toxin or other etiologic causes prior to labeling an adverse event as an irAE. Information on how to

identify and evaluate irAEs has been developed and is included in the Event of Clinical Interest and Immune-Related Adverse Event Guidance Document. See Section 12.6. Subjects who develop a Grade 2 or higher irAE should be discussed immediately with the Sponsor.

Recommendations to managing irAEs not detailed elsewhere in the protocol are detailed in Table 5.

Table 5 General Approach to Handling irAEs

irAE	Withhold/Discontinue Pembrolizumab?	Supportive Care
Grade 1	No action	Provide symptomatic treatment
Grade 2	May withhold pembrolizumab	Consider systemic corticosteroids in addition to appropriate symptomatic treatment
Grade 3 and Grade 4	Withhold pembrolizumab Discontinue if unable to reduce corticosteroid dose to < 10 mg per day prednisone equivalent within 12 weeks of toxicity	Systemic corticosteroids are indicated in addition to appropriate symptomatic treatment. May utilize 1 to 2 mg/kg prednisone or equivalent per day. Steroid taper should be considered once symptoms improve to Grade 1 or less and tapered over at least 4 weeks.

5.6.1.2 Supportive Care Guidelines for Pneumonitis

Subjects with symptomatic pneumonitis should immediately stop receiving pembrolizumab and have an evaluation. The evaluation may include bronchoscopy and pulmonary function tests to rule out other causes such as infection. If the subject is determined to have study drug associated pneumonitis, the suggested treatment plan is detailed in Table 6.

Table 6 Recommended Approach to Handling Pneumonitis

Study drug associated pneumonitis	Withhold/Discontinue Pembrolizumab?	Supportive Care
Grade 1 (asymptomatic)	No action	Intervention not indicated
Grade 2	Withhold pembrolizumab, may return to treatment if improves to Grade 1 or resolves within 12 weeks	Systemic corticosteroids are indicated. Taper if necessary.
Grade 3 and Grade 4	Discontinue pembrolizumab	Systemic corticosteroids are indicated. The use of infliximab may be indicated as appropriate. Refer to the Event of Clinical Interest and Immune-related Adverse Event Guidance Document for additional recommendations.

For Grade 2 pneumonitis that improves to ≤ Grade 1 within 12 weeks, the following rules should apply:

- First episode of pneumonitis
    - May increase dosing interval by one week in subsequent cycles
- Second episode of pneumonitis – permanently discontinue pembrolizumab if upon rechallenge subject develops pneumonitis ≥ Grade 2

5.7 Diet/Activity/Other Considerations

5.7.1 Diet

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

5.7.2 Contraception for participants and their female partners

It is not known if pembrolizumab has transient adverse effects on the composition of sperm. Participants, who for this study are male, are likely to be sterile because radical prostatectomy and external beam radiation to the prostate are akin to vasectomy, and subjects are highly unlikely to impregnate their partners. For those subjects who have intercourse with a premenopausal woman who is potentially able to conceive, their partners will be asked to use 2 methods of birth control. The two birth control methods can be either two barrier methods or a barrier method plus a hormonal method to prevent pregnancy. Female partners of subjects should start using birth control from study Visit 1 throughout the study period up to 120 days after the last dose of study therapy.

The following are considered adequate barrier methods of contraception: diaphragm, condom (by the partner), copper intrauterine device, sponge, or spermicide. Appropriate hormonal contraceptives will include any registered and marketed contraceptive agent that contains an estrogen and/or a progestational agent (including oral, subcutaneous, intrauterine, or intramuscular agents).

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 their partners must adhere to the contraception requirement (described above) for the duration of the study and during the follow-up period defined in section 7.2.2-Reporting of Pregnancy and Lactation to Dr. Graff at OHSU and to Merck. If there is any question that a subject will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

5.7.3 Pregnancy of Partner

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

5.8 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 after 12 weeks of treatment (see Table 7)

  Note: A subject may be granted an exception to continue on treatment with confirmed radiographic progression if clinically stable or clinically improved, but Dr. Graff must be contacted first. If the subject has continued radiographic progression after the next set of 4 treatments OR clinical deterioration (such as increased pain) during the treatment, he must be removed from the study.

- 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
- Administrative reasons

The End of Treatment and Follow-up visit procedures are listed in Section 6 (Protocol Flow Chart) and Section 7.1.5 (Visit Requirements). 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.

Patients will not be taken off study for PSA progression alone.

5.9 Subject Replacement Strategy

Subjects who do not receive a single dose of pembrolizumab will be replaced.

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

6.1 Study Flow Chart

Trial Period:						**Treatment Cycle[a]**									**End of Treatment**	**Post-Treatment**	
							Monitoring		Retreatment								
Treatment Cycle/Title:	Main Study Screening (Visit 1)	1	2	3	4	Post-first course (3 weeks after cycle 4)	Assess Every 6 weeks after "post first course/retreatment course"	Assess Every 12 weeks on study	1	2	3	4	Post retreatment course ((3 weeks after retreatment cycle 4)	Discontinuation (Discon)	Safety Follow-up	Survival Follow-Up
Scheduling Window (Days):	-28 to -1		± 3	± 3	± 3	± 3	± 3	±7	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days post discon*	Every 12 weeks ± 2 week
Informed Consent	X															
Inclusion/Exclusion Criteria	X															
Archival Tissue Collection	X															
Biopsy of Metastatic Lesion	X**					X***			X^				X***	X***[1]		
Demographics and Medical History	X															
Prior Medication Review	X	X	X	X	X	X	X		X	X	X	X	X			
Testosterone, Lactate DeHydrogenase	X															
Trial Treatment Administration (pembrolizumab)		X	X	X	X				X	X	X	X				
Enzalutamide, daily	X	X	X	X	X	X	X	X	X	X	X	X	X			
Review Adverse Events, include Events of Clinical Interest		X	X	X	X	X	X						X	X	X	

Trial Period:		**Treatment Cycle[a]**												**End of Treatment**	**Post-Treatment**	
							Monitoring		Retreatment					Discontinua-tion (Discon)		
Treatment Cycle/Title:	Main Study Screening (Visit 1)	1	2	3	4	Post-first course (3 weeks after cycle 4)	Assess Every 6 weeks after "post first course/retreatment course"	Assess Every 12 weeks on study	1	2	3	4	Post retreatment course ((3 weeks after retreatment cycle 4)		Safety Follow-up	Survival Follow-Up
Scheduling Window (Days):	-28 to -1		± 3	± 3	± 3	± 3	± 3	±7	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days post discon*	Every 12 weeks ± 2 week
Review Concomitant Medications	X	X	X	X	X	X	X		X	X	X	X	X	X	X	
Physical Examination	X	X	X	X	X	X	X		X	X	X	X	X	X	X	
Vital Signs and Weight	X	X	X	X	X	X	X		X	X	X	X	X	X	X	
ECOG Performance Status	X	X	X	X	X	X	X		X	X	X	X	X	X	X	
PSA	X	X	X	X	X	X	X		X	X	X	X	X	X	X	
PT/INR and aPTT, pre-biopsy only	X					X							X	X		
LDH		X														
CBC with Differential	X	X	X	X	X	X	X[1]		X	X	X	X	X	X	X	
Comprehensive Serum Chemistry Panel	X	X	X	X	X	X	X[1]		X	X	X	X	X	X	X	
Urinalysis	X	X	X	X	X	X	X[1]		X	X	X	X	X	X	X	
T3, FT4 and TSH	X	X	X	X	X	X	X[1]		X	X	X	X	X	X	X	
C Reactive Protein		X	X	X	X	X			X	X	X	X	X			
Tumor Imaging	X					X[£]		X[£]					X[£]			

[1] Investigator(s) may reduce the frequency of these tests for subjects in the monitoring phase who are at least 3 months removed from their last dose of pembrolizumab.

Trial Period:		**Treatment Cycle[a]**											**End of Treatment**	**Post-Treatment**	
							Monitoring		Retreatment						
Treatment Cycle/Title:	Main Study Screening (Visit 1)	1	2	3	4	Post-first course (3 weeks after cycle 4)	Assess Every 6 weeks after "post first course/retreatment course"	Assess Every 12 weeks on study	1	2	3	4	Post retreatment course ((3 weeks after retreatment cycle 4)	Discontinuation (Discon)	Safety Follow-up	Survival Follow-Up
Scheduling Window (Days):	-28 to -1		± 3	± 3	± 3	± 3	± 3	±7	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days post discon*	Every 12 weeks ± 2 week
Correlative Studies Blood Collection-PBMCs and Serum		X	X	X	X	X		X	X	X	X	X	X[μ]			
Correlative Studies Blood Collection-CTCs		X			X									X		
Correlative studies buccal swab, blood and/or tissue—NORMAl control [+]	X[**]					X[***]							X[***]	X[***1]		
Correlatives studies: Rectal Swab, Questionnaire[b], Mouth Swish		X	X	X	X	X		X	X	X	X	X				
Post-study anticancer therapy status															X	X
Survival Status		X	X	X	X	X	X		X	X	X	X	X	X	X	X

[a] Each Cycle is 3 weeks long, unless extended for toxicity in accordance with Section 5.2.1.2

* If a subject initiates a new anti-cancer therapy within 30 days after discontinuing the study, the 30 day Safety Follow-up visit must occur before the first dose of the new therapy.

**Does not necessarily have to be done within this 28 day period, but must be done prior to getting cycle 1.

***Does not necessarily have to be done within 3 days of post-first/retreatment course/discontinuation. We prefer it be done close to the post-first course, but it may be done any time after this point. If there is no lesion amenable to biopsy, this will have to be skipped.

£ +/- 7 day window. For subjects entering retreatment phase, imaging must be repeated prior to retreatment (RT) cycle 1 (unless imaging occurred less than 28 days prior to RT cycle 1). For subjects in the monitoring phase, imagining frequency may be decreased with investigator approval.
[l] If progression after a period of response or stability.
[µ] PBMCs only at this time point (do not collect serum sample)
[b] "General Gut Biome" questionnaire to be used at cycle 1 visit. The more truncated "Interval" questionnaire is to be used at other assessments.

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^ Prior to restarting pembrolizumab if there is a lesion to be safely biopsied.

7.0 TRIAL PROCEDURES

7.1 Trial Procedures

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

Furthermore, additional evaluations/testing may be deemed necessary by the Sponsor and/or Merck for reasons related to 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 Administrative Procedures

7.1.1.1 Informed Consent

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

7.1.1.1.1 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.

7.1.1.2 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.

7.1.1.3 Medical History

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

7.1.1.4 Prior and Concomitant Medications Review

7.1.1.4.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the 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.

7.1.1.4.2 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.

7.1.1.5 Disease Details and Treatments

7.1.1.5.1 Disease Details

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

7.1.1.5.2 Prior Treatment Details

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

7.1.1.5.3 Subsequent Anti-Cancer Therapy Status

The investigator or qualified designee will review all new anti-neoplastic therapy initiated after the last dose of trial treatment. If a 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.

7.1.1.6 Assignment of Subject ID Number

This is a single-site study. Subjects will receive a study code that is 11025-number when they are enrolled (deemed eligible) on the study. For example, the first subject is 11025-01.

7.1.1.7 This log will be submitted to the coordinating center on a regular basis. Assignment of Randomization Number

Not applicable, as this is not a randomized study.

7.1.1.8 Subject Registration

A centralized registration procedure will be used. After eligibility screening, subjects who are selected to participate will be registered with the Lead Center (OHSU). A record of patients who fail to meet entry criteria (i.e., screen failures) will be maintained. Subject registration must be completed before beginning any treatment or study activities.

7.1.1.8.1 Coordinating Center (OHSU) Registration

All participants will be registered with OHSU. Registration will be completed via electronic Clinical Research Information System (eCRIS). A copy of the signed consent, a completed Eligibility Checklist and other relevant information must be included in the Electronic Registration System.

7.1.1.8.2 Participating Sites

Central registration for this study will take place at Oregon Health & Science University (OHSU). Knight Cancer Institute

To complete registration and enroll a participant from another institution, the study staff at that site must contact the designated research staff at OHSU to notify him/her of the participant registration. The site staff then needs to fax or email registration/eligibility registration to:

Multicenter Study Manager:

Rachel Slottke Fax: 503.494.6197or Email: slottker@ohsu.edu

The following documentation must be sent for each enrollment:

- The completed Eligibility Checklist
- The signed informed consent and HIPAA Authorization form
- Supporting source documentation for eligibility questions (laboratory results, pathology report, radiology reports, MD notes, physical exams, medial history and prior treatment records.)

Upon receipt, the research staff at OSHU will conduct an interim review of all documents. If the participant meets all criteria, all source documentation is received, the participating site IRB has granted approval for the protocol and the site is in good standing with OHSU, the OHSU research staff will register the subject.

Once eligibility has been established and the participant is registered, the participant will be assigned a protocol participant number. This number is unique to the participant and must be written on all data and correspondence for the participant. This protocol participant number will be relayed back to study staff at the registering site via e-mail and will serve as the enrollment confirmation.

7.1.1.9 Institutional Registration

Subject registration at each study site/institution will be conducted according to the institution's established policies.

7.1.1.10 Trial Compliance (Medication/Diet/Activity/Other)

Subjects will fill out a medication diary describing their daily use of enzalutamide. The study team will review the medication diary at each visit.

7.1.2 Clinical Procedures/Assessments

7.1.2.1 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 Section 12.2). Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

All AEs of unknown etiology associated with pembrolizumab exposure should be evaluated to determine if it is possibly an event of clinical interest (ECI) of a potentially immunologic etiology (irAE). See Section 5.6.1.1 regarding the identification, evaluation and management of AEs of a potential immunological etiology.

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

7.1.2.2 Full Physical Exam

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

7.1.2.3 Directed Physical Exam

N/A

7.1.2.4 Vital Signs

The investigator or qualified designee will take vital signs at screening, prior to the administration of each dose of trial treatment and at treatment discontinuation as specified in the Trial Flow Chart (Section 6.0). Vital signs should include temperature, pulse, respiratory rate, weight and blood pressure. Height will only be measured before the first trial treatment (screening or Cycle 1 Day 1 pre-infusion).

7.1.2.5 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG status (see Section 12.4) at screening, prior to the administration of each dose of trial treatment and discontinuation of trial treatment as specified in the Trial Flow Chart. After Cycle 8 assessment of ECOG status will be performed in conjunction with the physical exam.

7.1.2.6 Tumor Imaging and Assessment of Disease

To ensure a uniform tumor assessment schedule, regular radiological imaging (eg, MRI/CT of chest, abdomen, pelvis, plus other nodal disease as applicable, and bone scans) will be performed for all subjects at Screening and Week 12. Subjects that have not met the Treatment Stopping Criteria specified in Section 5.8 will continue tumor assessments at Week 24, and every 12 weeks thereafter. Frequency of tumor assessments may be decreased with investigator approval once a patient is no longer receiving pembrolizumab.

All disease progression should be confirmed with a repeat tumor assessment at least 6 weeks after the initial progression assessment. See Table 7 for a detailed description of disease progression.

Subjects that enter the Toxicity/Progression Follow-up Phase without confirmed PD will have tumor assessments performed as specified in Section 7.1.2.6.

Pembrolizumab acts by increasing the magnitude of the immune response against tumor associated antigens. However, it is well described that such an immune response might take weeks, if not months, to fully mobilize the immune system before resulting in a clinically observable effect. Prior to this time, some subjects with CRPC may experience an increase in their level of PSA before the immune response is able to control the progression of their disease. PSA may then start to decline as the immune response effectively reduces the tumor burden. Due to the time it may take for a pembrolizumab-mediated immune response to take effect, PSA values obtained prior to Week 12 will not be considered in the determination of disease progression.

It is also expected that a tumor flare might be observed at sites of disease on CT/MRI/bone scan,

even in the absence of tumor cell growth, since an intense immune response may take place at these sites due to the mechanism of action of pembrolizumab. Since this tumor flare may present upon radiologic assessment as an increase in tumor volume, it is strongly recommended that such assessments NOT be performed prior to Week 12, unless the subject is experiencing clinical deterioration that is indicative of possible disease progression.

This study proposes to perform radiologic tumor assessments, consisting of MRI/CT and bone scans, at 12-week intervals, starting at Week 12. The start of radiologic follow-up at Week 12 after pembrolizumab therapy accounts for the unique immunological mechanism and is consistent with The Prostate Cancer Clinical Trials Working Group 2 (PCWG2) recommendations of a "protocol-specified minimum exposure of 12 weeks" to study therapy, in order to ensure that study drug is not discontinued before it has had a chance to work.(31)

7.1.2.7 Definitions of Measurable and Non-measurable Lesions and Disease

See Section 12.3. Measurable and Non-measurable disease is defined by RECIST 1.1.

7.1.2.8 Definition of Target, Non-Target Lesions

See Section 12.3.

7.1.2.9 New Lesions

See Table 7 for a description of the determination of progression based on the presence of new lesions.
Note: The appearance of a new lesion does not by itself satisfy the criteria for confirmed progressive disease. Rather, the tumor burden imposed by the new lesion must be evaluated within the context of the total tumor burden (pre-existing plus new lesions). Confirmation of progression in Target lesions, Non-target (non-bone) lesions, and Bone lesions require 2 assessment time points. The first of these (TP1) must occur at Week 12 or later with the second (TP2) occurring at least 6 weeks later. Progression declared at TP1 remains unconfirmed unless TP2 demonstrates continuing or worsening progression as described in Section 7.1.2.11.See section 12.3 for more information regarding soft tissue disease.

7.1.2.10 Method of Tumor Response Assessment

If, due to a radioisotope shortage, your imaging facility is unable to perform a Technetium-99 (Tech-99) bone scan at a protocol-specified time point, then the following scanning options may be used:

- Full body CT
- Full body MRI
- Fluoride PET

7.1.2.11 Disease Progression Criteria

At each disease assessment, progression (PD) will be determined using the criteria in Table 7. For treatment guidance, and for the purpose of efficacy assessments, confirmation PD is required. The

rationale for confirmation of PD is based on recommendations fromthe Prostate Cancer Working Group 2 (PCWG2): "Therapy may be prematurely discontinued if outcome measures do not reflect disease status accurately. As noted, bone scans in particular, are relatively insensitive in the early follow-up period. Consideration of drug pharmacodynamics is also important. For example, a successful vaccination might produce a lymphocytic infiltrate in a tumor mass that would transiently increase its size giving the false impression of worsening disease. To avoid misinterpreting these early results, PCWG2 asserts that any post-treatment change in disease status, be it favorable or unfavorable, be confirmed using a second assessment at a later time point."(32)

Therefore, confirmation of progression in PSA requires 3 assessment time points. Confirmation of progression in Target lesions, Non-target (non-bone) lesions, and Bone lesions requires 2 assessment time points. The first of these (TP1) must occur at Week 12 or later with the second (TP2) occurring at least 6 weeks later. Progression declared at TP1 remains unconfirmed unless TP2 demonstrates continuing or worsening progression as described below:

PSA: The first PSA at week 12 or after must demonstrate a ≥ 25% increase and ≥ 2 ng/ml increase above nadir (TP1). PSA progression at TP1 remains unconfirmed unless followed by a confirmed rising trend in 2 subsequent PSA values. PSA at TP2 must be > PSA at TP1.

Note: Since PSA values obtained between week 1 and week 12 are not considered when determining progression, they cannot be used as nadir.

- Target and Non-target (non-bone) lesions: Use RECIST 1.1 for progression, with additional requirements that progression at first assessment (TP1) be confirmed by a second scan 6 or more weeks later. See Section 12.3 for information about soft tissue disease.
- Bone lesions: Assessment at TP1 must demonstrate the appearance of 2 or more new lesions. Progression at TP1 remains unconfirmed unless the TP2 assessment demonstrates the appearance of an additional 2 or more lesions when compared to TP1. After TP1 the appearance of 2 or more new lesions need to be confirmed with an additional scan 6 or more weeks later. The subsequent scan must show persistence of previous lesions or additional new lesions.

Note: If unconfirmed progression noted at TP1 is not confirmed at TP2, the next assessment time point after TP1 that meets the criteria for progression is treated as TP1.

Table 7: Definition of Disease Progression

Disease Parameter	Unconfirmed Progression Time Point 1 (TP1)	Confirmed Progression	Date of Progression

PSA (requires 2 measurements)[a]	≥ 25% increase and ≥ 2 ng/ml increase above the nadir (Ignore PSA prior to week 12)	PSA continues to climb 3 weeks after the first progression	TP1
Target Lesions (CT/MRI) Section 12.3 for soft tissue disease assessment	≥ 20% increase in the sum of diameters of target lesions. The sum must also demonstrate an absolute increase of at least 5mm. Or the appearance of one or more new lesions ≥ Week 12	TP2 Sum of diameters of TP2 ≥ Sum of diameters of TP1 Confirmation of radiographic progression is not required for soft tissue after Week 12	TP1
Non-Target Lesions (non-bone) (CT/MRI)	Unequivocal progression of existing non-target lesions (The appearance of one or more new lesions is also considered progression) See Section 12.3 for more information.	TP 2 Continued progression of non-target lesions Confirmation of radiographic progression is not required for soft tissue after Week 12	TP1
Bone (Bone scan/X-ray)	Appearance of ≥ 2 new lesions	TP2 Appearance of ≥ 2 new lesions compared to TP1 After Week 12 the appearance of two new lesions need to be confirmed 6 or more weeks later. The confirmatory scan must show	TP1

		persistence of previous lesions or additional new lesions	
Clinical Deterioration	Clinical Deterioration at any time (defined as Persistent decrease in performance status (eg, lasting for more than 14 days) of at least 2 points from baseline, attributable to disease progression) Any time		Date of Clinical Deterioration

a Since PSA values obtained between week 1 and week 12 are not considered when determining progression, they cannot be used as nadir.

Definition of PSA and Radiographic Stability. Neither response nor progression.

7.1.2.12 Disease Response Criteria

PSA decrease of at least 50%.

Radiographic Response will be determined using RECIST 1.1.(33)

See Section 12.3.

7.1.2.13 Tumor Tissue Collection and Correlative Studies Blood Sampling

For all subjects, we will request the tumor block or 10 unstained slides from the initial diagnosis, such as biopsy or from radical prostatectomy. In addition, for subjects with a biopsy accessible metastatic deposit, we will collect 6 tissue cores. Blood (100 mL) will be collected just prior to pembrolizumab at each dose. See Appendices 12.4 and 12.5 for additional details.

7.1.2.14 Normal Tissue Collection

Normal tissue can be collected from any non-tumor source, including whole blood (20 mLs), normal tissue collected during study biopsy or during non-study procedure (surgical discard), skin, or saliva. Our plan is to collect whole blood on patients (20 mLs) during screening, treatment, or non-treatment follow-up. However, if non-cancer tissue has already been collected (study biopsy or other procedure) and is available, we will use that tissue in lieu of an additional blood draw.

7.1.3 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below. Please contact the sponsor for details concerning the total amount of blood/tissue to be drawn/collected over the course of the trial (from pre-trial to post-trial visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per subject.

7.1.3.1 Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

Laboratory tests for hematology, chemistry, urinalysis, and others are specified in Table 8. Please contact the sponsor for details concerning the total amount of blood/tissue to be drawn/collected over the course of the trial (from pre-trial to post-trial visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per subject can be found in Sections 12.4 and 12.5.

Table 8 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 per institutional standard)	Aspartate aminotransferase (AST)	Specific gravity	Free tyroxine (T4)
Red Blood Cell Count	Carbon Dioxide ‡		Thyroid stimulating hormone (TSH)
Absolute Neutrophil Count	*(CO_2 or bicarbonate)*		C Reactive Protein
	Calcium		Blood for correlative studies
	Chloride		Lactate Dehydrogenase (LDH)
	Glucose		
	Creatinine		
	Potassium		
	Sodium		
	Total Bilirubin		
	Direct Bilirubin *(If total bilirubin is elevated above the upper limit of normal)*		
	Total protein		
	Blood Urea Nitrogen		
	Blood Urea Nitrogen		

Laboratory tests for screening or prior to retreatment should be performed within 28 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.

7.1.3.2 Pharmacokinetic/Pharmacodynamic Evaluations

7.1.3.2.1 Blood and Tissue Collection for Correlative Work and Serum Pembrolizumab

See Appendices 12.4 and 12.5 for details.

PK data will not be done for this study. PK analysis has been done on previous studies with pembrolizumab. The PK is not changed by chemotherapy or other concomitant medications. This is not surprising considering it is an antibody.

7.1.3.2.2 Blood Collection for Anti-Pembrolizumab Antibodies

Sample collection, storage and shipment instructions for blood samples are provided in Section 12.4.

7.1.4 Other Procedures

7.1.4.1 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. After discontinuing treatment following assessment of CR, these subjects should return to the site for a Safety Follow-up Visit (described in Section 7.1.5.3.1) and then proceed to the Follow-Up Period of the study (described in Section 7.1.5.4).

7.1.4.2 Blinding/Unblinding. This is an open label study.

7.1.5 Visit Requirements

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

7.1.5.1 Screening

7.1.5.1.1 Screening Period

The screening period begins at the time of consent and lasts 28 days. During this time, subjects will undergo imaging studies (CT and NM bone scan) and blood work to ensure they are suitable candidates. They will also undergo a biopsy if they have a lesion amenable to biopsy. Assessments

completed prior to consenting for clinical purposes (such as CT or Bone scans, or blood work) will not be required to be repeated if they are within the 28 day screening period.

7.1.5.2 Treatment Period

All subjects will receive four doses of pembrolizumab, unless they withdraw from the study. No official assessments of response will occur during these treatments, even though the PSA will be drawn. Those subjects who have stable disease or a disease response by PSA or imaging at 12 weeks can go on to receive additional treatments until disease progression. Those subjects who have clearly progressive disease after the initial four treatments will not be retreated with pembrolizumab.

7.1.5.3 Post-Treatment Visits

7.1.5.3.1 Safety Follow-Up Visit

The mandatory Safety Follow-Up Visit should be conducted approximately 30 days after the end of treatment visitor 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.

7.1.5.4 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 (84 ± 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 7.1.5.2. 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 7.1.5.2 will move from the follow-up phase to the Second Course Phase when they experience disease progression. Details are provided in Section 6.2 – Trial Flow Chart for Retreatment. Of note, it is possible to be retreated indefinitely.

7.1.5.4.1 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.

7.2 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.

For laboratory abnormalities, the criteria for determining whether an abnormal test finding should be reported as an adverse event are as follows:

- Test result is associated with accompanying symptoms, and/or
- Test result requires additional diagnostic testing or medical/surgical intervention, and/or
- Test result leads to a change in study dosing outside of protocol-stipulated dose adjustments or discontinuation from the study, significant additional concomitant drug treatment, or therapy, and/or
- Test result is considered to be an adverse event by the Investigator

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 within the follow-up period specified by the protocol, or prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal.

Adverse events may also occur in screened subjects during any pre-allocation baseline period as a result of a protocol-specified intervention, including washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

All adverse events will be recorded from the time the consent form is signed through 30 days following cessation of treatment and 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.

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. If the subject requires a blood draw, fresh tumor biopsy etc., the subject is first required to provide consent to the main study and AEs will be captured according to guidelines for standard AE reporting.

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 will be defined as any dose exceeding the prescribed dose for pembrolizumab by 20% over the prescribed dose. No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, pembrolizumab should be discontinued and 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; FAX 215 993-1220)

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 of a male subject's female partner that occurs during the trial or within 120 days of completing the trial completing the trial, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier. All female partners of male subjects who become pregnant 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.

From the time these events become known to the study team, they must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220)

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 a new cancer (that is not a condition of the study);
- Is associated with an overdose;
- Is any other important medical event

Refer to Table 9 for additional details regarding each of the above criteria.

Progression of the cancer under study is not considered an adverse event unless it results in hospitalization or death.

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 that occurs to any subject from the time the consent is signed through 90 days following cessation of treatment, or the initiation of new anti-cancer therapy, whichever is earlier, whether or not related to Merck product, must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety. The clock begins at the time the study team learns of the event.

Non-serious Events of Clinical Interest will be forwarded to the Sponsor (OHSU) and to Merck Global Safety and will be handled in the same manner as SAEs.

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 outside of the time period specified in the previous paragraph also must be reported immediately to the Sponsor and to Merck.

SAE reports and any other relevant safety information are to be forwarded to the Merck Global Safety facsimile number: +1-215-993-1220

A copy of all 15 Day Reports and Annual Progress Reports is submitted as required by FDA, European Union (EU), Pharmaceutical and Medical Devices agency (PMDA) or other local regulators. Investigators will cross reference this submission according to local regulations to the Merck Investigational Compound Number (IND, CSA, etc.) at the time of submission. Additionally investigators will submit a copy of these reports to Merck & Co., Inc. (Attn: Worldwide Product Safety; FAX 215 993-1220) at the time of submission to FDA.

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

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 recorded as such on the Adverse Event case report forms/worksheets and reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220)

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. The trial site guidance for assessment and follow up of these criteria can be found in the Investigator Trial File Binder (or equivalent).

3. In the event a subject develops any of the following AEs, a detailed narrative of the event should be reported as an ECI to the Sponsor within 24 hours and to Merck Global Safety within 2 working days of the event:

   a. Grade ≥ 3 diarrhea
   b. Grade ≥ 2 colitis
   c. Grade ≥ 2 pneumonitis
   d. Grade ≥ 3 hypo- or hyperthyroidism

A separate guidance document has been provided entitled “event of Clinical Interest and Immune-Related Adverse Event Guidance Document.” This document provides guidance regarding identification, evaluation and management of ECIs and irAEs. Additional ECIs are identified in this guidance document and also need to be reported to the Sponsor within 24 hours and to Merck Global Safety within 2 working days of the event.

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

ECIs that occur in any subject from the date of first dose through 90 days following cessation of treatment, or the initiation of a new anticancer therapy, whichever is earlier, whether or not related to the Merck's product, must be reported within 24 hours to the Sponsor and to Merck Global Safety within 2 working days.

7.2.3.3 Responsibility of Participating Sites

Participating sites are responsible for reporting all SAEs to their local IRB per local guideline.

Participating sites are responsible for reporting all SAEs and Events of Clinical Interest to OHSU via fax or email within 24 hours of becoming aware of the event. Please see section 7.2.3.1 and 7.2.3.2.

Responsibility of OHSU

The OHSU research staff is responsible for submitting all SAEs/UPs to the OHSU IRB.

The OHSU research staff is responsible for submitting all SAEs and Events of Clinical Interest to Merck Global Safety.

The OHSU PI is responsible for informing all participating sites about all SAEs.

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 9 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 [including hospitalization for an elective procedure] for a preexisting condition which has not worsened does not constitute a serious adverse event.); 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) **or**	
	Is an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event. 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.	
	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 the Merck product to be discontinued?	
Relationship to test drug	Did the Merck product cause the adverse event? The determination of the likelihood that the 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 the Merck product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Merck product caused the adverse event (AE):	
	Exposure	Is there evidence that the subject was actually exposed to the 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 the 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 the 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 Merck product; or (3) the trial is a single-dose drug trial); or (4) Merck product(s) is/are only used one time.)
	Rechallenge	Was the subject re-exposed to the 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) Merck 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 THE MERCK PRODUCT, OR IF REEXPOSURE TO THE MERCK PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE SUBJECT, THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE U.S. CLINICAL MONITOR 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 the 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 a Merck product relationship).**	
Yes, there is a reasonable possibility of Merck product relationship.	There is evidence of exposure to the Merck product. The temporal sequence of the AE onset relative to the administration of the Merck product is reasonable. The AE is more likely explained by the Merck product than by another cause.	
No, there is not a reasonable possibility Merck product relationship	Subject did not receive the Merck product OR temporal sequence of the AE onset relative to administration of the Merck product is not reasonable OR there is another obvious cause of the AE. (Also entered for a subject with overdose without an associated AE.)	

7.2.5 Responsibility for Reporting Adverse Events

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

8.0 STATISTICAL ANALYSIS PLAN

This is a single-arm phase II clinical trial to examine the efficacy of pembrolizumab in men with mCRPC who initially responded to single-agent enzalutamide but who are currently experiencing a PSA progression.

8.1 Primary and Secondary Endpoints

Primary endpoint: PSA response, defined by a PSA decrease of at least 50% confirmed by a second measurement at least 3 weeks later.

Secondary endpoints:

- % change in PSA
- Immunological parameters, including leukocytes, lymphocytes (CD8+, CD4+, and B cells), and macrophages in prostate tissue at diagnosis (if original biopsy is available) and pre-treatment.
- Immunohistochemisty for PD-1, PD-L1 and PD-L2 in prostate tissue at diagnosis (if original biopsy is available) and pre-treatment
- Circulating tumor cells (CTCs) (binary variable)
- Changes in T cell numbers, activation, and phenotype as measured in PBMC at diagnosis and throughout therapy, including T effector/memory panel (CD45, CD3, CD8, CCR7, CD45RA,CD45RO, CD69, CD44, CD62L), T regulatory panel (CD45, CD3, CD4, FoxP3, CD25, CD127, CD69, CD44), T help panel (CD45, CD3, CD4, CD45RA, CD45RO, CD69, CD44, CD62L), and cytokine propensity of the above T cell subsets (IFN-γ, IL-2, IL-4, IL-12, IL-13, IL-10, IL-18, TNF-α, TGF-β, IL-17)
- Systemic inflammatory markers: Serum IL-8, IL-6, IL-1, TNF and TGF-beta
- Objective disease response by radiographs
- Overall survival
- PSA progression free survival where the definition of progression will be PSA progression per Prostate Cancer Working Group 2 criteria. If there is a decline from baseline, progression is an increase in PSA that is 25% and 2 ng/ml above the nadir, which is confirmed by a second value 3 or more weeks later (i.e., a confirmed rising trend)

- DNA mutations.

8.2 Statistical Analysis Plan

Descriptive statistical analysis will be conducted for all primary and secondary endpoints, for all patients, and for subgroups (abiraterone versus no prior abiraterone and sipuleucel-T versus no prior sipuleucel-T). The proportion estimate will be reported with 95% confidence interval, and the continuous variables will be summarized using nmissing, mean, std, median, min, and max. Safety and adverse events will be presented in a tabular form.

One-sample binomial test will be used to assess whether the proportion of PSA response (PSA decrease of at least 50%) is significantly greater than 0.05. Univariable logistic regression analysis will be conducted to assess the association between immunological parameters and PSA response responses. Scale in logit will be assessed for all continuous parameters that are identified to be significantly associated with PSA response. Our hypothesis is that Microsatellite instability and PD-L1 expression together with other immunological parameters are potential predictors for PSA response. As the incidence of MSI and the presence of PD-L1 expression are relatively small (under 10% for MSI), we propose to enroll 30 additional subjects to this study to help find 1) whether MSI and PD-L1 expression are likely predictors for PSA response and 2) whether any other immunological parameters independently or jointly predicts the PSA response. Multivariable logistic regression model will be fitted to identify the potential predictors. Stepwise variable selection will be used to find the final model. Random forest will also be used as a parallel method for building the predictive model. The area under the Receiver Operating Characteristic (ROC) curve will be computed for the discrimination ability of the predictive model. 10-fold cross validation will be performed to assess the validation of the proposed model. Due to the limited sample size, we will not have a separate testing set to validate the predictive model. Therefore, all findings are exploratory and need to be validated. Kaplan-Meier curve will be plotted to illustrate the PSA progression free survival for all, and for subgroups (abiraterone versus no prior abiraterone and sipuleucel-T versus no prior sipuleucel-T).

8.3 Sample Size Computation

Patients with PSA progression on treatment are extremely unlikely to have a PSA response without a change in therapy. If 25% of subjects treated with pembrolizumab upon progression with enzalutamide have a PSA response, this therapy would be worthy of further study. Using a null hypothesis of 5% and alternate hypothesis of 25%, 25 evaluable patients are needed with 90% power and a one-sided alpha of 0.05. To account for potential drop-out, we will enroll 28 subjects.

We propose to add 30 additional subjects to this study (for a total of 58) to better evaluate the association between PSA responses and candidate risk factors (MSI and PD-L1 expression with other immunological parameters), and to build a prognostic model. The proposed sample size will achieve 80% power to detect AUC of 0.85 against AUC of 0.6 using two-sided z test at 5% significance level. We understand that it is not guaranteed that a predictive model with good predictive ability can be constructed, because both MSI and PD-L1 expressions are relatively rare. However, the collected data and analysis will be clinically valuable to help us determine whether a future larger study is worthy. . In the initial study, we did biopsies on any subject that had a

metastatic lesion that could be biopsied, but subjects were not required to have a lesion that could be biopsied. We are doing biopsies on all 30 additional patients along with the tests we did on earlier participants.

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 10.

Table 10 Product Descriptions

Product Name & Potency	Dosage Form
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

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

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 at the trial site.

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

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

10.1 Confidentiality

Patient confidentiality will be protected by keeping all hard copies in a locked file cabinet or in a locked room, on a protected floor that only allows access to those with the appropriate badge. Any information stored on a computer will be behind the OHSU firewall. HIPAA procedures will also be followed.

10.2 Compliance with Financial Disclosure Requirements

Funds given to investigators will be reported via the Sunshine Act by Merck.

10.3 Compliance with Law, Audit and Debarment

This trial will be conducted in compliance with all applicable institutional, local, and federal regulations. This includes auditing by appropriate regulatory authorities if necessary.

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 Quality Management System

OHSU Knight Cancer Institute, through the auditing function of the Knight Clinical Trials Office, is responsible for ensuring that all member investigators and affiliate investigators conduct clinical research studies in compliance with local IRB standards, FDA regulations and NIH policies and in accordance with the Data and Safety Monitoring Plan policies and procedures http://ozone.ohsu.edu/cancer/sharedres/kctoresdocs.cfm

Locally initiated studies will be audited by OHSU Knight CI Auditor. Newly approved studies may be audited anytime after enrollment has been initiated. Each OHSU Knight approved treatment protocol will be audited on an annual basis in accordance with the Knight Data and Safety Monitoring Plan.

It is the responsibility of each participating site's principal investigator to ensure that the study is conducted in compliance with local IRB standards, FDA regulations, and NIH policies. It is also the responsibility of each site's principal investigator to ensure that quality assurance audits at their site are conducted according to their institution's policies and procedures. The quality assurance audit process provides assurance that reported data accurately reflects the data in the primary subject record.

10.6 Data Management

The Sponsor will be responsible for developing data collection tools such as Case Report Forms (CRF), Study Management Tools, and a database if appropriate. Data required to meet the objectives of this protocol will be collected via CRF and transmitted in a secure fashion. A Study-Specific Data Monitoring Plan (SsDMP) will be developed as a separate document for both the Lead Site and any participating Sub-sites. Risk based monitoring will be utilized, with remote monitoring of source documentation and protocol compliance. At the discretion of the Sponsor, monitoring or auditing in addition to that outlined in the SsDMP may be conducted.

10.7 Inclusion of Women, Children and Minorities

No OHSU Knight Cancer Institute study will focus on any particular racial or ethnic subset. No subject will be excluded from the study on the basis of racial or ethnic origin. Male and minority volunteers will be recruited for this study from the general population and 100% men will be studied.

The racial and ethnic composition of the study should represent that of the state of Oregon (see Table 11). If the prevalence of the disease being studied is consistent across race, ethnicity and gender, then these figures can be used to calculate projected enrollments in Table 12. If the disease being studied does *not* affect both genders or all races and ethnicities equally (e.g., cervical cancer only affects women and Black males are more likely than White males to have prostate cancer), then this information should be taken into account when calculating the projected enrollment. The OHSU General Clinical Research Center has links to various sources of statistics on their webpage at www.ohsu.edu/gcrc. If a different source is used in calculating projected enrollments, that source should be cited below Table 2.

Table 11: Population Demographics - Oregon (%)

Ethnic Category	Sex/Gender		
	Females	Males	Total
Hispanic or Latino			11.7
Not Hispanic or Latino			88.3

Ethnic Category	Sex/Gender		
	Females	Males	Total
Ethnic Category: Total of all subjects*			100*
Racial Category			
American Indian or Alaskan Native			1.4
Asian			3.7
Black or African American			1.8
Native Hawaiian or other Pacific Islander			0.3
White			83.6
More than one race			3.8
Unknown/Other			5.3
Racial Category: Total of all subjects*			100*
TOTALS	50.4	49.6	100*

Source: U.S. Census Bureau, 2010 *Totals may not equal 100 due to rounding.

Table 12: Projected Accrual for the Present Study

Ethnic Category	Sex/Gender			
	Females	Males	Unknown	Total
Hispanic or Latino	0	2	0	
Not Hispanic or Latino	0	26	0	
Unknown	0	0	0	
Ethnic Category: Total of all subjects*	0	28	0	28*
Racial Category				

Ethnic Category	Sex/Gender			
	Females	Males	Unknown	Total
American Indian or Alaskan Native	0	0-1	0	
Asian	0	0-1	0	
Black or African American	0	0-1	0	
Native Hawaiian or other Pacific Islander	0	0-1	0	
White	0	26	0	
More than one race	0	0-1	0	
Unknown	0	0-2	0	
Racial Category: Total of all subjects*	0	28	0	28*

Source: Adapted from U.S. Census Bureau, 2010 *Totals may not equal 100 due to rounding.

This protocol does not include children for the following reason: Prostate cancer does not affect children under the age of 18.

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12.0 APPENDICES

12.1 ECOG Performance Status

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

12.2 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)

12.3 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 response. 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 the 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.

In addition, volumetric analysis will be explored by central review for response assessment.

12.4 Correlative Work –Contact study sponsor for information regarding collection, processing, and shipping of blood and tissue.

12.5 Biopsy of Metastatic Lesion

Due to the nature of metastatic prostate cancer, most biopsies will be from bone. This biopsy is being done for the correlative endpoints (see section 4.2.3.2). Bone biopsies present unique challenges with respect to the collection and processing. However, regardless of collection technique, rapid freezing of the biopsy material is critical to subsequent success. As part of the trial, we will provide kits to each site enrolling patients so as to facilitate a standardized collection of tissue.

Patients are positioned by radiology and conscious sedation may be administered to improve patient comfort. This is based on the judgment of the interventional radiologist and may be restricted in some centers due to the availability of supportive services.

During the image-guided biopsy procedure we recommend the following general rules when choosing a metastatic site and a specific location within the metastatic tumor for biopsy:

1) If the patient has bone only disease, the pelvis is the preferred site for biopsy.
2) Any biopsy kit capable of obtaining core biopsies from bone is acceptable. The Bonopty Coaxial biopsy system with eccentric drill (http://www.vasocare.co.kr/product04-5.html).http://www.vasocare.co.kr/product04-5.html) is a recommended system. Internal diameter is 1.3mm. This is the smallest for collection of usable material.
3) In the bone, extremely blastic lesions seldom yield usable material. Yields are greater if biopsies are performed in marrow of abnormal signal intensity directly adjacent to blastic lesions. Often, we pass the needle tangential to the blastic lesion in the marrow space for our most successful collections.
4) In soft tissue, do not biopsy from regions of metastatic lesions that appear necrotic on CT or MRI due to extremely poor yield.
5) It is important that excessive compressive force is not required or used to expel the biopsy from the biopsy needle. This obscures cellular morphology. If it is difficult to expel the biopsy from the core needle, alternative biopsy kits should be used.

Please follow the directions below when processing the biopsy material:

Required Materials

Included in Kit:
• Disposable cryo-molds 15x15x5mm
• Sakura Tissue-Tek OCT compound
• Metal plate or tray

• Sarstedt black permanent marker
• Tissue-Tek Mega-Cassettes
• Styrofoam cooler
• Container of neutral buffered formalin (2 provided, keep extra, an additional vial will be included with the new box)

*Keep all remaining materials after procedure is completed for use on future biopsies unless otherwise noted

Not Included (should be available on site)
• Dry Ice (pellet form, smaller pellet size works best)
• Syringe needle (core manipulation; ≤19g)
• Forceps (fine toothed)

Protocol for Biopsies
1. Prepare a cold working surface by filling the supplied styrofoam cooler container roughly half full of dry ice. Shake the container to form a fairly even layer.
2. Place the metal sheet or tray into the cooler and allow it to cool below -10°C. Temperatures below this point will freeze OCT compound quickly, facilitating the block formation. Having a flat metallic surface is also important.

3. Prior to heading to the collection, place several cryomolds on the cold metal surface allowing them to cool down prior to the biopsy.

4. Label 5 tissue cassettes, then place on dry ice to pre-chill before use during the procedure.

5. Take the cooler setup to the location of the biopsy and be sure to have easy access to it during the procedure. Be sure to take the formalin vial in the zip-lock bag as well.

6. Once the radiologist says a core is about ready, fill one of the cryomold trays roughly half-full of OCT so that the compound is partially frozen by the time the core is added. The OCT compound will appear opaque as it solidifies.

7. Transfer a core to the partially solidified OCT layer in the cryomold. The best method of tissue transfer from the biopsy needle to the pallet will depend on the type of needle used. The core biopsy can be directly placed into the cryomold of OCT, but care must be taken to ensure the core is lying as close to flat as possible as it freezes. Bonopty and other hollow core needles will yield a cylindrical core that is ejected via a plunger needle. The pressure created by the plunger directly onto the core can unpredictably eject the core from the needle. If the core cannot be placed directly on the OCT, it can be ejected onto a gauze pad and transferred immediately onto the OCT so as to minimize time for RNA degradation and protein de-phosphorylation. This helps to maintain needle sterility and allows for more careful manipulation of the core away from the sterile procedure cart. Manipulation of the core from gauze pad to cryomold is done with a syringe needle.

8. Positioning of the core is very important. Be sure to place the core flat down on the center of the OCT layer. The tissue can freeze on contact if the OCT layer has solidified, thus preventing manipulation once the tissue is on the OCT surface. Adding the core to OCT prior to solidification is ideal since the tissue and OCT will then freeze at the same time, resulting in better sectioning later. Layers frozen in different stages tend to cause separation during sectioning.

9. Immediately cover the core with OCT, working in a slow circular motion around the core such that OCT fills in the sides, then surrounds the top. Contact of the liquid OCT with the tissue core is important to preserve the tissue and facilitate in cryo sectioning later.

10. Once the OCT becomes opaque in each cryomold, the tissue block is ready to be transferred to the labeled cold cassette.

11. In addition to collecting fresh-frozen biopsy cores, 2 core must be collected for paraffin embedding. This core should be placed in the container of neutral buffered formalin. Close the jar tightly, and return to the zip-lock bag.

12. Package the biopsies into the provided insulated box. The cold cryo cassettes should be placed in dry ice in the insulated section of the box, and the formalin vial contained within the zip-lock bag should be placed outside of the insulated region of the box. The appropriate spot for the formalin vial will be labeled.

13. Include with the shipment, the sample shipment log that should include comments regarding core quality (long cylindrical core, bone shards, mostly blood clot, etc), the quantity of cores and any irregularities in the freezing process. The technician performing the collection should be sure to note their unique patient ID, the biopsy date, and the time of the procedure as well.

14. Prior to any shipments, the study coordinator and designated laboratory staff at OHSU must be notified. Notification should come in the form of email at least 2 – 3 days or, if possible, a week prior to an anticipated shipment. The email should consist of the date of scheduled biopsy, unique patient ID, participating site name and site contact; this should be sent to Specimen Manager.

15. Mail by Express Overnight delivery to the address specified on the provided shipping labels. Unless special arrangements are made, do not ship on Fridays, Saturdays, or Sundays.

12.6 Event of Clinical Interest and Immune-Related Adverse Event Guidance Document

PEMBROLIZUMAB PROGRAM (MK-3475)

EVENT OF CLINICAL INTEREST

GUIDANCE DOCUMENT

Version 5.0

REVISION HISTORY LOG

Version	Effective Date*	Revision Author	Action
1	08-Aug-2012	Kevin Gergich	Initial Release of guidance document for MK-3475
2	07-June-2013	Marty Huber, Kevin Gergich, Holly Brown	Revised title, formerly was "MK-3475 Immune-Related Adverse Event Identification, Evaluation and Management Guidance Document for Investigators" Revised the format of irAE Guidance document, including layout, font, sectioning, etc. for consistency with Sponsor Events of Clinical Interest guidance documents. Modified Categories for irAEs: – Replaced GI with Colitis category. – Removed Neurologic category. – Added Renal category. Removed detail in the irAE Guidance document that can be located in the Investigator's Brochure for MK-3475. Removed details regarding non-MK-3475 compounds. Added ECI reporting guidelines. Included a Table Events of Clinical Interest: Immune-Related Adverse Events that includes the key terms. – Also placed a pull-out quick-review sheet in the Appendix. Updated background, diagnosis and course of treatment details for irAEs.

3	10-Sep-2014	Marty Huber, Kevin Gergich, Holly Brown	Renamed the document: "Pembrolizumab Program (MK-3475) - Events of Clinical Interest Guidance Document". Introduced generic name: pembrolizumab (MK-3475) and inserted throughout the document. Updated Overview – Section 1 - Clarified the scope of the document and the reporting window for ECIs - Updated Table 1 with medDRA Preferred Terms for adverse events to correspond with reporting of terms to clinical database, rearranged the order, and updated the reporting criteria. - Updated the dose modification/discontinuation section to clarify discontinuation and hold terminology. Updated Section 2 – ECI Reporting Guidelines

			– Clarified that ECIs must be reported to Merck **within 24 hours** regardless of attribution to study treatment or etiology. Updated Section 3 – For All Sections, removed the Course of Action for Grade 1 events. - Section 3.1 Pneumonitis – Moved Pneumonitis to beginning of ECI Section – Updated management guidelines for Grade 2 and Grade 3-4 events - Section 3.2 Colitis: - Updated AE terms and ECI criteria, updated course of action language for clarity - Section 3.3 Endocrine: - Updated ECI criteria and updated course of action language for clarity. - Added subsections for hypophysitis, hyperthyroidism and hypothyroidism to clarify management guidelines. - Section 3.4 Hematologic: - New section added. - Section 3.5: Hepatic: - Updated terms and added additional guidance for reporting of DILI ECI; updated course of action for clarity - Section 3.6 Neurologic: - New section added. - Section 3.7 Ocular: - Changed the name of this section from Eye to Ocular - Added the term “iritis”, updated ECI guidance, and updated course of action language for clarity - Section 3.8 Renal: - Updated section for clarity. - Section 3.9 Skin: - Updated list of terms and added terms for reporting of other skin ECIs; added section 3.9.1: Immediate Evaluation for Potential Skin ECIs - Section 3.10 Other: - Updated list of terms for clarity; revised course of action for clarity.

			- Section 3.11 Infusion Reactions: - New section added. - Section 3.12: Follow-up to Resolution: - New section added. - Section 4: - References updated. - Section 5: - ECI table updated for consistency with Table 1. - Section 6: Appendix 2 – Past Medical History Related to Dermatologic Event: New section added. - Section 7: Appendix 3 – Presentation of the Dermatologic Event: New section added. - Section 8: Appendix 4 – Focused Skin Examination: New section added.
4	04-Dec-2014	Scot Ebbinghaus, Oswaldo Bracco, Holly Brown, Kevin Gergich	- Table 1 - Updated Endocrine (reported as ECI if ≥ Grade 3 or ≥ Grade 2 and resulting in dose modification or use of systemic steroids to treat the AE) Section to include: - Hyperglycemia, if ≥Grade 3 and associated with ketosis or metabolic acidosis (DKA) - Created new section in Table 1 – Endocrine (reported as ECI) and added: - Type 1 diabetes mellitus (if new onset) - Hepatic: Clarified Transaminase elevations as: - Transaminase elevations (ALT and/or AST) - Section 3.2 Colitis - Updated the duration of diarrhea requirments under the Course of Action for Grade 2 and Grade 3 - Section 3.3 Endocrine - Clarified Course of Action for hyperthyroidism and hypothyroidism - Added Course of Action section for Type 1 diabetes mellitus (if new onset) and ≥ Grade 3 hyperglycemia - Section 5 - Updated Reference Table in Appendix 1
5	18-Dec-2014	Holly Brown Kevin Gergich	- Section 3.3 Endocrine - Updated the Course of Action for Hypophysitis - Merged Grades 2-4 into one course of action

*Ensure that you are using the most current version of this document.

TABLE OF CONTENTS

1. OVERVIEW

The purpose of this document is to provide study sites with guidance on the identification and management of Events of Clinical Interest for the MK-3475 (also known as pembrolizumab) program.

Based on the literature review [1-11], and consideration of mechanism of action of pembrolizumab, potential immune-related adverse events (irAEs) are the primary Event of Clinical Interest (ECI). Immune-related AEs are adverse events associated with the treatment of patients with immunotherapy treatments that appear to be associated with the immune therapy's mechanism of action. Based on these potential irAEs, the sponsor has defined a list of specific adverse event terms (ECIs) that are selected adverse experiences that **must be reported to Merck within 24 hours** from the time the Investigator/physician is aware of such an occurrence, regardless of whether or not the investigator/physician considers the event to be related to study drug(s). In addition, these ECIs require additional detailed information to be collected and recorded. ECIs may be identified through spontaneous patient report and / or upon review of subject data. **Table 1** provides the list of terms and reporting requirements for AEs that must be reported as ECIs for MK-3475 protocols. Of note, the requirement for reporting of ECIs applies to all arms, including comparators, of MK- 3475 clinical trials

Given that our current list of events of clinical interest is not comprehensive for all potential immune-related events, it is possible that AEs other than those listed in this document may be observed in patients receiving pembrolizumab. Therefore any Grade 3 or higher event that the investigator/physician considers to be immune-related should be reported as an ECI regardless of whether the specific event term is in Table 1 **and reported to Merck within 24 hours** from the time the Investigator/physician is aware of such an occurrence. Adverse events that are both an SAE and an ECI should be reported one time as an SAE only, however the event must be appropriately identified as an ECI and recorded.

Table 1: Events of Clinical Interest

Pneumonitis (reported as ECI if ≥ Grade 2)		
Acute interstitial pneumonitis	Interstitial lung disease	Pneumonitis
Colitis (reported as ECI if ≥ Grade 2 or any grade resulting in dose modification or use of systemic steroids to treat the AE)		
Intestinal Obstruction	Colitis	Colitis microscopic
Enterocolitis	Enterocolitis hemorrhagic	Gastrointestinal perforation
Necrotizing colitis	Diarrhea	
Endocrine (reported as ECI if ≥ Grade 3 or ≥ Grade 2 and resulting in dose modification or use of systemic steroids to treat the AE)		
Adrenal Insufficiency	Hyperthyroidism	Hypophysitis
Hypopituitarism	Hypothyroidism	Thyroid disorder
Thyroiditis	Hyperglycemia, if ≥Grade 3 and associated with ketosis or metabolic acidosis (DKA)	
Endocrine (reported as ECI)		
Type 1 diabetes mellitus (if new onset)		
Hematologic (reported as ECI if ≥ Grade 3 or any grade resulting in dose modification or use of systemic steroids to treat the AE)		
Autoimmune hemolytic anemia	Aplastic anemia	Thrombotic Thrombocytopenic Purpura (TTP)
Idiopathic (or immune) Thrombocytopenia Purpura (ITP)	Disseminated Intravascular Coagulation (DIC)	Haemolytic Uraemic Syndrome (HUS)
Any Grade 4 anemia regardless of underlying mechanism		
Hepatic (reported as ECI if ≥ Grade 2, or any grade resulting in dose modification or use of systemic steroids to treat the AE**)**		
Hepatitis	Autoimmune hepatitis	Transaminase elevations (ALT and/or AST)
Infusion Reactions (reported as ECI for any grade)		
Allergic reaction	Anaphylaxis	Cytokine release syndrome
Serum sickness	Infusion reactions	Infusion-like reactions
Neurologic (reported as ECI for any grade)		
Autoimmune neuropathy	Guillain-Barre syndrome	Demyelinating polyneuropathy
Myasthenic syndrome		
Ocular (report as ECI if ≥ Grade 2 or any grade resulting in dose modification or use of systemic steroids to treat the AE)		
Uveitis	Iritis	
Renal (reported as ECI if ≥ Grade 2)		
Nephritis	Nephritis autoimmune	Renal Failure
Renal failure acute	Creatinine elevations (report as ECI if ≥Grade 3 or any grade resulting in dose modification or use of systemic steroids to treat the AE)	
Skin (reported as ECI for any grade)		
Dermatitis exfoliative	Erythema multiforme	Stevens-Johnson syndrome
Toxic epidermal necrolysis		
Skin (reported as ECI if ≥ Grade 3)		
Pruritus	Rash	Rash generalized
Rash maculo-papular		
Any rash considered clinically significant in the physician's judgment		
Other (reported as ECI for any grade)		
Myocarditis	Pancreatitis	Pericarditis
Any other Grade 3 event which is considered immune-related by the physician		

Each of the events above is described within this guidance document, along with site requirements for reporting these events to the Sponsor. The information collected should be entered into the narrative field(s) of the Adverse Event module in the database (please note, if narrative entry into the database is not available, please use the narrative text box on the 1727/AER Form). If additional Medical History or Concomitant Medications are reported, the Medical History and Concomitant Medication modules in the database must be updated.

In addition, the guidelines include recommendations on the management of these ECIs. These guidelines are intended to be applied when the physician determines the events to be related to pembrolizumab. Note: if after the evaluation the event is determined not to be related, the physician is instructed to follow the ECI reporting guidance but does not need to follow the treatment guidance (below). Therefore, these recommendations should be seen as guidelines and the treating physician should exercise individual clinical judgment based on the patient. For any question of dose modification or other treatment options, the specific language in the protocol should be followed. Any questions pertaining to the collection of this information or management of ECIs should be directed to your local Sponsor contact.

Dose Modification/Discontinuation

The treatment guidance provides specific direction when to hold and/or discontinue pembrolizumab for each immune related adverse event. Of note, when the guidance states to "discontinue" pembrolizumab this is the permanent discontinuation of treatment with pembrolizumab. "Hold" means to stop treating with pembrolizumab but resumption of treatment may be considered assuming the patient meets the criteria for resumption of treatment.

2. ECI REPORTING GUIDELINES

ECIs are selected non-serious and serious adverse experiences that must be reported to Merck **within 24 hours** regardless of attribution to study treatment. The AEs listed in this document and any event that meets the ECI criteria (as noted) in Table 1 or in the respective protocol (event term and Grade) must be reported regardless of physician-determined causality with study medication and whether or not considered immune-related by the physician (unless otherwise specified). Physicians/study coordinators/designated site personnel are required to record these experiences as ECIs on the Adverse Experience electronic Case Report Forms (eCRFs) (or on paper) and to provide supplemental information (such as medical history, concomitant medications, investigations, etc.) about the event.

- Please refer to the Data Entry Guidelines (DEGs) for your protocol.
- Please refer to protocol for details on reporting timelines and reporting of Overdose and Drug Induced Liver Injury (DILI).

3. ECI CATEGORIES AND TERMS

This section describes the ECI categories and outlines subject management guidelines when an ECI is reported.

3.1 Pneumonitis

The following AE terms, if considered ≥ Grade 2, are considered ECIs and should be reported to the Sponsor within 24 hours of the event:

- Pneumonitis
- Interstitial lung disease
- Acute interstitial pneumonitis

If symptoms indicate possible new or worsening cardiac abnormalities additional testing and/or a cardiology consultation should be considered.

All attempts should be made to rule out other causes such as metastatic disease, bacterial or viral infection**. It is important that patients with a suspected diagnosis of pneumonitis be managed as per the guidance below until treatment-related pneumonitis is excluded. Treatment of both a potential infectious etiology and pneumonitis in parallel may be warranted. Management of the treatment of suspected pneumonitis with steroid treatment should not be delayed for a therapeutic trial of antibiotics.** If an alternative diagnosis is established, the patient does not require management as below; however the AE should be reported regardless of etiology.

Course of Action

Grade 2 events:
- Report as ECI
- Hold pembrolizumab.
- Consider pulmonary consultation with bronchoscopy and biopsy/BAL.
- Consider ID consult
- Conduct an in person evaluation approximately twice per week
- Consider frequent Chest X-ray as part of monitoring
- Treat with systemic corticosteroids at a dose of 1 to 2 mg/kg/day prednisone or equivalent. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
- Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.
- Second episode of pneumonitis – discontinue pembrolizumab if upon re-challenge the patient develops a second episode of Grade 2 or higher pneumonitis.

Grade 3 and 4 events:
- Report as ECI
- Discontinue pembrolizumab.
- Hospitalize patient
- Bronchoscopy with biopsy and/or BAL is recommended.
- Immediately treat with intravenous steroids (methylprednisolone 125 mg IV). When symptoms improve to Grade 1 or less, a high dose oral steroid (prednisone 1 to 2 mg/kg once per day or dexamethasone 4 mg every 4 hours) taper should be started and continued over no less than 4 weeks.
- If IV steroids followed by high dose oral steroids does not reduce initial symptoms within

48 to 72 hours, treat with additional anti-inflammatory measures. Discontinue additional anti-inflammatory measures upon symptom relief and initiate a prolonged steroid taper over 45 to 60 days. If symptoms worsen during steroid reduction, initiate a retapering of steroids starting at a higher dose of 80 or 100 mg followed by a more prolonged taper and administer additional anti-inflammatory measures, as needed

– Add prophylactic antibiotics for opportunistic infections.

3.2 Colitis

The following AE terms, if considered ≥ Grade 2 or resulting in dose modification or use of systemic steroids to treat the AE, are considered ECIs and should be reported to the Sponsor within 24 hours of the event:

- Colitis
- Colitis microscopic
- Enterocolitis
- Enterocolitis hemorrhagic
- Gastrointestinal perforation
- Intestinal obstruction
- Necrotizing colitis
- Diarrhea

All attempts should be made to rule out other causes such as metastatic disease, bacterial or parasitic infection, viral gastroenteritis, or the first manifestation of an inflammatory bowel disease by examination for stool leukocytes, stool cultures, a Clostridium difficile titer and endoscopy. However the AE should be reported regardless of etiology.

Course of Action

Grade 2 Diarrhea/Colitis (4-6 stools/day over baseline, dehydration requiring IV fluids < 24 hours, abdominal pain, mucus or blood in stool):

- Report as ECI
- Hold pembrolizumab.
- Symptomatic Treatment
- For Grade 2 diarrhea that persists for greater than 3 days, and for diarrhea with blood and/or mucus,
    - Consider GI consultation and endoscopy to confirm or rule out colitis
    - Administer oral corticosteroids (prednisone 1-2 mg/kg QD or equivalent)
- When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
- Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.
- If symptoms worsen or persist > 3 days treat as Grade 3

Grade 3 Diarrhea/Colitis (or Grade 2 diarrhea that persists for > 1 week):

- Report as ECI
- Hold pembrolizumab.
- Rule out bowel perforation. Imaging with plain films or CT can be useful.
- Recommend consultation with Gastroenterologist and confirmation biopsy with endoscopy.
- Treat with intravenous steroids (methylprednisolone 125 mg) followed by high dose oral steroids (prednisone 1 to 2 mg/kg once per day or dexamethasone 4 mg every 4 hours) When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Taper over 6 to 8 weeks in patients with diffuse and severe ulceration and/or bleeding.
- Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of

prednisone or equivalent per day within 12 weeks.

– If IV steroids followed by high dose oral steroids does not reduce initial symptoms within 48 to 72 hours, consider treatment with additional anti-inflammatory measures as described in the literature [5]. Discontinue additional anti-inflammatory measures upon symptom relief and initiate a prolonged steroid taper over 45 to 60 days. If symptoms worsen during steroid reduction, initiate a retapering of steroids starting at a higher dose of 80 or 100 mg followed by a more prolonged taper and administer additional anti-inflammatory measures as needed.

Grade 4 events:

- Report as ECI
- Permanently discontinue pembrolizumab.
- Manage as per Grade 3.

3.3 Endocrine

The following AE terms, if considered ≥Grade 3 or if ≥Grade 2 and require holding/discontinuation/ modification of pembrolizumab dosing, are considered ECIs and should be reported to the Sponsor within 24 hours of the event:

- Adrenal insufficiency
- Hyperthyroidism
- Hypophysitis
- Hypopituitarism
- Hypothyroidism
- Thyroid disorder
- Thyroiditis

All attempts should be made to rule out other causes such as brain metastases, sepsis and/or infection. However the AE should be reported regardless of etiology.

Hypophysitis or other symptomatic endocrinopathy other than hypo- or hyperthyroidism

Grade 2-4 events:

- Report as ECI if appropriate
- Hold pembrolizumab
- Rule out infection and sepsis with appropriate cultures and imaging.
- Monitor thyroid function or other hormonal level tests and serum chemistries more frequently until returned to baseline values.
- Pituitary gland imaging should be considered (MRIs with gadolinium and selective cuts of the pituitary can show enlargement or heterogeneity and confirm the diagnosis).
- Treat with prednisone 40 mg p.o. or equivalent per day. 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.
- Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.
- Hypophysitis with clinically significant adrenal insufficiency and hypotension, dehydration, and electrolyte abnormalities (such as hyponatremia and hyperkalemia) constitutes adrenal crisis.
- Consultation with an endocrinologist may be considered.

Hyperthyroidism and Hypothyroidism

Thyroid disorders can occur at any time during treatment and within three months of the last dose of pembrolizumab. 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, Grade 2-4 hypothyroidism events:

- Report as ECI if appropriate (see Table 1)
- Monitor thyroid function or other hormonal level tests and serum chemistries more frequently until returned to baseline values.
- Thyroid hormone and/or steroid replacement therapy to manage adrenal insufficiency.
- Therapy with pembrolizumab can be continued while treatment for the thyroid disorder is instituted.
- 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.
- Consultation with an endocrinologist may be considered.

Grade 3 hyperthyroidism events:

- Report as ECI
- Hold pembrolizumab.
- Rule out infection and sepsis with appropriate cultures and imaging.
- Treat with an initial dose of methylprednisolone 1 to 2 mg/kg intravenously followed by oral prednisone 1 to 2 mg/kg per day. 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.
- Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.

Grade 4 hyperthyroidism events:

- Report as ECI
- Discontinue pembrolizumab.
- Manage as per Grade 3

Type 1 diabetes mellitus (if new onset) and ≥ Grade 3 Hyperglycemia

The following AE terms are considered ECIs and should be reported to the Sponsor within 24 hours of the event:

- Type I diabetes mellitus (T1DM), if new onset, including diabetic ketoacidosis (DKA)
- Grade 3 or higher hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis (DKA).

Immune-mediated diabetes may present as new onset of Type 1 diabetes or an abrupt worsening of pre-existing diabetes associated with laboratorial evidence of beta cell failure. All attempts should be made to rule out other causes such as type 2 diabetes mellitus (T2DM), T2DM decompensation, steroid-induced diabetes, physiologic stress-induced diabetes, or poorly controlled pre-existing diabetes (either T1DM or T2DM), but events meeting the above criteria should be reported as ECIs regardless of etiology. The patients may present with hyperglycemia (abrupt onset or abrupt decompensation) with clinical evidence of diabetic ketoacidosis or laboratory evidence of insulin deficiency, such as ketonuria, laboratory evidence of metabolic acidosis, or low or undetected c-peptide.

Course of Action

T1DM should be immediately treated with insulin.

T1DM or Grade 3-4 Hyperglycemia events:

- Report as ECI if appropriate (see Table 1)
- Hold pembrolizumab for new onset Type 1 diabetes mellitus or Grade 3-4 hyperglycemia associated with evidence of beta cell failure, and resume pembrolizumab when patients are clinically and metabolically stable.
- 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.
- Consultation with an Endocrinologist is recommended.
- Consider local testing for islet cell antibodies and antibodies to GAD, IA-2, ZnT8, and insulin may be obtained.

3.4 Hematologic

The following AE term, if considered Grade ≥3 or requiring dose modification or use of systemic steroids to treat the AE, are considered an ECI and should be reported to the Sponsor within 24 hours of the event:

- Autoimmune hemolytic anemia
- Aplastic anemia
- Disseminated Intravascular Coagulation (DIC)
- Haemolytic Uraemic Syndrome (HUS)
- Idiopathic (or immune) Thrombocytopenia Purpura (ITP)
- Thrombotic Thrombocytopenic Purpura (TTP)
- Any Grade 4 anemia regardless of underlying mechanism

All attempts should be made to rule out other causes such as metastases, sepsis and/or infection. Relevant diagnostic studies such as peripheral blood smear, reticulocyte count, LDH, haptoglobin, bone marrow biopsy or Coomb's test, etc., should be considered to confirm the diagnosis. However the AE should be reported regardless of etiology.

Course of Action

Grade 2 events:
- Report as ECI
- Hold pembrolizumab
- Prednisone 1-2 mg/kg daily may be indicated
- Consider Hematology consultation.
  Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.

Grade 3 events:
- Report as ECI
- Hematology consultation.
- Hold pembrolizumab Discontinuation should be considered as per specific protocol guidance.
- Treat with methylprednisolone 125 mg iv or prednisone 1-2 mg/kg p.o. (or equivalent) as appropriate
- Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.

Grade 4 events:
- Report as ECI
- Hematology consultation
- Discontinue pembrolizumab for all solid tumor indications; refer to protocol for hematologic malignancies.
- Treat with methylprednisolone 125 mg iv or prednisone 1-2 mg/kg p.o. (or equivalent) as appropriate

3.5 Hepatic

The following AE terms, if considered ≥ Grade 2 or greater (or any grade with dose modification or use of systemic steroids to treat the AE), are considered ECIs and should be reported to the Sponsor within 24 hours of the event:

- Autoimmune hepatitis
- Hepatitis
- Transaminase elevations

All attempts should be made to rule out other causes such as metastatic disease, infection or other hepatic diseases. However the AE should be reported regardless of etiology.

Drug Induced Liver Injury (DILI)

In addition, the event must be reported as a Drug Induced Liver Injury (DILI) ECI, if the patient meets the laboratory criteria for potential DILI defined as:

- An elevated alanine transaminase (ALT) or aspartate transaminase (AST) lab value that is greater than or equal to three times (3X) the upper limit of normal (ULN) and
- An elevated total bilirubin lab value that is greater than or equal to two times (2X) ULN and
- At the same time, an alkaline phosphatase (ALP) lab value that is less than 2X ULN,
- As a result of within-protocol-specific testing or unscheduled testing.

Note that any hepatic immune ECI meeting DILI criteria should only be reported once as a DILI event.

Course of Action

Grade 2 events:

- Report as ECI
- Hold pembrolizumab when AST or ALT >3.0 to 5.0 times ULN and/or total bilirubin >1.5 to 3.0 times ULN.
- Monitor liver function tests more frequently until returned to baseline values (consider weekly).
  - Treat with 0.5-1 mg/kg/day methylprednisolone or oral equivalent and when LFT returns to grade 1 or baseline, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume pembrolizumab per protocol
- Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.
- Permanently discontinue pembrolizumab for patients with liver metastasis who begin treatment with Grade 2 elevation of AST or ALT, and AST or ALT increases ≥50% relative to baseline and lasts ≥1 week.

Grade 3 events:

- Report as ECI
- Discontinue pembrolizumab when AST or ALT >5.0 times ULN and/or total bilirubin >3.0 times ULN.
- Consider appropriate consultation and liver biopsy to establish etiology of hepatic injury, if necessary
- Treat with high-dose intravenous glucocorticosteroids for 24 to 48 hours. When symptoms

improve to Grade 1 or less, a steroid taper with dexamethasone 4 mg every 4 hours or prednisone at 1 to 2 mg/kg should be started and continued over no less than 4 weeks.

- If serum transaminase levels do not decrease 48 hours after initiation of systemic steroids, oral mycophenolate mofetil 500 mg every 12 hours may be given. Infliximab is not recommended due to its potential for hepatotoxicity.

- Several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased.
- Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.

Grade 4 events:

- Report as ECI
- Permanently discontinue pembrolizumab
- Manage patient as per Grade 3 above

3.6 Neurologic

The following AE terms, regardless of grade, are considered ECIs and should be reported to the Sponsor within 24 hours of the event:

- Autoimmune neuropathy
- Demyelinating polyneuropathy
- Guillain-Barre syndrome
- Myasthenic syndrome

All attempts should be made to rule out other causes such as metastatic disease, other medications or infectious causes. However the AE should be reported regardless of etiology.

Course of Action

Grade 2 events:
- Report as ECI
- Moderate (Grade 2) – consider withholding pembrolizumab.
- Consider treatment with prednisone 1-2 mg/kg p.o. daily as appropriate
- Consider Neurology consultation. Consider biopsy for confirmation of diagnosis.
- Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.

Grade 3 and 4 events:
- Report as ECI
- Discontinue pembrolizumab
- Obtain neurology consultation. Consider biopsy for confirmation of diagnosis
- Treat with systemic corticosteroids at a dose of 1 to 2 mg/kg prednisone or equivalent once per day. If condition worsens consider IVIG or other immunosuppressive therapies as per local guidelines

When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

3.7 Ocular

The following AE terms, if considered Grade ≥2 or requiring dose modification or use of systemic steroids to treat the AE, is considered an ECI and should be reported to the Sponsor within 24 hours of the event:

- Uveitis
- Iritis

All attempts should be made to rule out other causes such as metastatic disease, infection or other ocular disease (e.g. glaucoma or cataracts). However the AE should be reported regardless of etiology.

Course of Action

Grade 2 events:
- Evaluation by an ophthalmologist is strongly recommended.
- Treat with topical steroids such as 1% prednisolone acetate suspension and iridocyclitics.
- Discontinue pembrolizumab as per protocol if symptoms persist despite treatment with topical immunosuppressive therapy.

Grade 3 events:
- Evaluation by an ophthalmologist is strongly recommended
- Hold pembrolizumab and consider permanent discontinuation as per specific protocol guidance.
- Treat with systemic corticosteroids such as prednisone at a dose of 1 to 2 mg/kg per day. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
- Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.

Grade 4 events:
- Evaluation by an ophthalmologist is strongly recommended
- Permanently discontinue pembrolizumab.
- Treat with corticosteroids as per Grade 3 above

3.8 Renal

The following AEs if ≥ Grade 2 are considered ECIs and should be reported to the Sponsor within 24 hours of the event:

- Nephritis
- Nephritis autoimmune
- Renal failure
- Renal failure acute

Creatinine elevations ≥ Grade 3 or any grade with dose modification or use of systemic steroids to treat the AE.

All attempts should be made to rule out other causes such as obstructive uropathy, progression of disease, or injury due to other chemotherapy agents. A renal consultation is recommended. However the AE should be reported regardless of etiology.

Course of Action

Grade 2 events:
- Hold pembrolizumab
- Treatment with prednisone 1-2 mg/kg p.o. daily.
- Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.

Grade 3-4 events:
- Discontinue pembrolizumab
- Renal consultation with consideration of ultrasound and/or biopsy as appropriate
- Treat with systemic corticosteroids at a dose of 1 to 2 mg/kg prednisone IV or equivalent once per day.

When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

3.9 Skin

Rash and Pruritus

The following AEs should be considered as ECIs, if ≥ Grade 3 and should be reported to the Sponsor within 24 hours of the event:

- Pruritus
- Rash
- Rash generalized
- Rash maculo-papular
- In addition to CTCAE Grade 3 rash, any rash that is considered clinically significant, in the physician's judgment, should be treated as an ECI. Clinical significance is left to the physician to determine, and could possibly include rashes such as the following:
  - rash with a duration >2 weeks; OR
  - rash that is >10% body surface area; OR
  - rash that causes significant discomfort not relieved by topical medication or temporary cessation of study drug.

Other Skin ECIs

The following AEs should **always** be reported as ECIs, regardless of grade, and should be reported to the Sponsor within 24 hours of the event:

- Dermatitis exfoliative
- Erythema multiforme
- Steven's Johnson syndrome
- Toxic epidermal necrolysis

Please note, the AE should be reported regardless of etiology.

Course of Action

Grade 2 events:
- Symptomatic treatment should be given such as topical glucocorticosteroids (e.g., betamethasone 0.1% cream or hydrocortisone 1%) or urea-containing creams in combination with oral anti-pruritics (e.g., diphenhydramine HCl or hydroxyzine HCl).
- Treatment with oral steroids is at physician's discretion for Grade 2 events.

Grade 3 events:
- Hold pembrolizumab.
- Consider Dermatology Consultation and biopsy for confirmation of diagnosis.
- Treatment with oral steroids is recommended, starting with 1 mg/kg prednisone or equivalent once per day or dexamethasone 4 mg four times orally daily. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
- Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.

Grade 4 events:

- Permanently discontinue pembrolizumab.
- Dermatology consultation and consideration of biopsy and clinical dermatology photograph.
- Initiate steroids at 1 to 2 mg/kg prednisone or equivalent. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

3.9.1. Immediate Evaluation for Potential Skin ECIs

A. Photographs:
Every attempt should be made to get a photograph of the actual ECI skin lesion or rash as soon as possible**. Obtain appropriate consent for subject photographs if a consent form addendum is required by your IRB/ERC.**

- Take digital photographs of:
  - the head (to assess mucosal or eye involvement),
  - the trunk and extremities, and
  - a close-up of the skin lesion/rash.

- If possible, a ruler should be placed alongside the site of a skin occurrence as a fixed marker of distance.
- The time/date stamp should be set in the 'ON' position for documentation purposes.
- Photographs should be stored with the subject's study records.
- The Sponsor may request copies of photographs. The local study contact (e.g., CRA) will provide guidance to the site, if needed.

B. Past Medical History:
Collect past medical history relevant to the event, using the questions in Appendix 2 (Past Medical History Related to Dermatologic Event) as a guide. Any preexisting conditions not previously reported (e.g., drug allergy) should be entered into the Medical History eCRF.

C. Presentation of the Event:
Collect information on clinical presentation and potential contributing factors using the questions in Appendix 3 (Presentation of the Dermatologic Event) as a guide. This information should be summarized and entered in narrative format in the AE eCRF. Please use the available free-text fields, such as Signs and Symptoms. Note pertinent negatives where applicable to reflect that the information was collected. Any treatments administered should be entered on the Concomitant Medication eCRF.

D. Vitals Signs and Standard Laboratory Tests:
Measure vital signs (pulse, sitting BP, oral temperature, and respiratory rate) and record on the Vital Signs eCRF. Perform standard laboratory tests (CBC with manual differential and serum chemistry panel, including LFTs).

E. Focused Skin Examination:
Perform a focused skin examination using the questions in Appendix 4 (Focused Skin Examination) as a guide. Information should be summarized and entered on the Adverse Experience eCRF as part of the narrative.

F. Dermatology Consult
Refer the subject to a dermatologist as soon as possible.

- For a **"severe rash"**, the subject must be seen within **1-2 days** of reporting the event.
- For **clinically significant rash**, the subject should be seen within **3-5 days**.

The dermatologist should submit a biopsy sample to a certified dermatopathology laboratory or to a pathologist experienced in reviewing skin specimens.

The site should provide the dermatologist with all relevant case history, including copies of clinical photographs and laboratory test results.

3.10 Other

The following AEs, regardless of grade, are considered ECIs and should be reported to the Sponsor within 24 hours of the event:

- Myocarditis
- Pericarditis
- Pancreatitis
- Any additional Grade 3 or higher event which the physician considers to be immune related

All attempts should be made to rule out other causes. Therapeutic specialists should be consulted as appropriate. However the AE should be reported regardless of etiology.

Course of Action

Grade 2 events or Grade 1 events that do not improve with symptomatic treatment:
- Withhold pembrolizumab.
- Systemic corticosteroids may be indicated.
- Consider biopsy for confirmation of diagnosis.
- If pembrolizumab held and corticosteroid required, manage as per grade 3 below.

Grade 3 events:
- Hold pembrolizumab
- Treat with systemic corticosteroids at a dose of 1 to 2 mg/kg prednisone or equivalent once per day.
- When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
- Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks. Otherwise, pembrolizumab treatment may be restarted and the dose modified as specified in the protocol

Grade 4 events:
- Treat with systemic corticosteroids at a dose of 1 to 2 mg/kg prednisone or equivalent once per day.
- Discontinue pembrolizumab

3.11 Infusion Reactions

The following AE terms, regardless of grade, are considered ECIs and should be reported to the Sponsor within 24 hours of the event:

- Allergic reaction
- Anaphylaxis
- Cytokine release syndrome
- Serum sickness
- Infusion reactions
- Infusion-like reactions

Please note, the AE should be reported regardless of etiology.

Course of Action

Refer to infusion reaction table in the protocol and below.

Infusion Reactions

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.** 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 with: Diphenhydramine 50 mg p.o. (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg p.o. (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. For Further information, please refer to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE) at http://ctep.cancer.gov		

3.12 Follow-up to Resolution

Subjects should be followed to resolution. The Adverse Experience eCRF should be updated with information regarding duration and clinical course of the event. Information obtained from the consulting specialist, including diagnosis, should be recorded in the appropriate AE fields. Free-text fields should be used to record narrative information:

- Clinical course of the event
- Course of treatment
- Evidence supporting recovery
- Follow-up to the clinical course

Any treatments administered for the event should also be entered in the Concomitant Medication eCRF.

4. REFERENCES

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5. APPENDIX 1 –Events of Clinical Interest (ECI) – Reference Table

Pneumonitis (reported as ECI if ≥ Grade 2)		
Acute interstitial pneumonitis	Interstitial lung disease	Pneumonitis
Colitis (reported as ECI if ≥ Grade 2 or any grade resulting in dose modification or use of systemic steroids to treat the AE)		
Intestinal Obstruction	Colitis	Colitis microscopic
Enterocolitis	Enterocolitis hemorrhagic	Gastrointestinal perforation
Necrotizing colitis	Diarrhea	
Endocrine (reported as ECI if ≥ Grade 3 or ≥ Grade 2 and resulting in dose modification or use of systemic steroids to treat the AE)		
Adrenal Insufficiency	Hyperthyroidism	Hypophysitis
Hypopituitarism	Hypothyroidism	Thyroid disorder
Thyroiditis	Hyperglycemia, if ≥Grade 3 and associated with ketosis or metabolic acidosis (DKA)	
Endocrine (reported as ECI)		
Type 1 diabetes mellitus (if new onset)		
Hematologic (reported as ECI if ≥ Grade 3 or any grade resulting in dose modification or use of systemic steroids to treat the AE)		
Autoimmune hemolytic anemia	Aplastic anemia	Thrombotic Thrombocytopenic Purpura (TTP)
Idiopathic (or immune) Thrombocytopenia Purpura (ITP)	Disseminated Intravascular Coagulation (DIC)	Haemolytic Uraemic Syndrome (HUS)
Any Grade 4 anemia regardless of underlying mechanism		
Hepatic (reported as ECI if ≥ Grade 2, or any grade resulting in dose modification or use of systemic steroids to treat the AE**)**		
Hepatitis	Autoimmune hepatitis	Transaminase elevations (ALT and/or AST)
Infusion Reactions (reported as ECI for any grade)		
Allergic reaction	Anaphylaxis	Cytokine release syndrome
Serum sickness	Infusion reactions	Infusion-like reactions
Neurologic (reported as ECI for any grade)		
Autoimmune neuropathy	Guillain-Barre syndrome	Demyelinating polyneuropathy
Myasthenic syndrome		
Ocular (report as ECI if ≥ Grade 2 or any grade resulting in dose modification or use of systemic steroids to treat the AE)		
Uveitis	Iritis	
Renal (reported as ECI if ≥ Grade 2)		
Nephritis	Nephritis autoimmune	Renal Failure
Renal failure acute	Creatinine elevations (report as ECI if ≥Grade 3 or any grade resulting in dose modification or use of systemic steroids to treat the AE)	
Skin (reported as ECI for any grade)		
Dermatitis exfoliative	Erythema multiforme	Stevens-Johnson syndrome
Toxic epidermal necrolysis		
Skin (reported as ECI if ≥ Grade 3)		
Pruritus	Rash	Rash generalized
Rash maculo-papular		
Any rash considered clinically significant in the physician's judgment		
Other (reported as ECI for any grade)		
Myocarditis	Pancreatitis	Pericarditis
Any other Grade 3 event which is considered immune-related by the physician		

6. APPENDIX 2 – Past Medical History Related to Dermatologic Event

Past Medical History:
Any preexisting conditions not previously reported (e.g., drug allergy) should be entered into the Medical History eCRF.

1. Does the subject have any allergies? □ Yes □ No If

yes, please obtain the following information:

a. Any allergy to drugs (including topical or ophthalmic drugs)? □ Yes □ No

List the drug name(s) and describe the type of allergic response (e.g. rash, anaphylaxis, etc):

_____

_____

b. Any allergy to external agents, such as laundry detergents, soaps, poison ivy, nickel, etc.? □ Yes □ No

Describe the agent and type of allergic response: _____

_____

c. Any allergy to food? □ Yes □ No

Describe the food and type of allergic response: _____

_____

d. Any allergy to animals, insects? □ Yes □ No

Describe the allergen and type of allergic response: _____

_____

e. Any other allergy? □ Yes □ No

Describe the allergen and type of allergic response: _____

_____

2. Does the subject have any other history of skin reactions, skin eruptions, or rashes? □ Yes □ No

If so what kind? _____

3. Has the subject ever been treated for a skin condition? □ Yes □ No

If so what kind? _____

4. Is the current finding similar to a past experience? □ Yes □ No

7. APPENDIX 3 – Presentation of the Dermatologic Event

Presentation of the event:
Collect information on clinical presentation and potential contributing factors. Key information should be summarized and entered on the Adverse Experience eCRF. Any treatments administered should be entered on the Concomitant Medication eCRF.

1. What is the onset time of the skin reaction, skin eruption, or rash relative to dose of study drug?

_____

2. Has the subject contacted any known allergens? □ Yes □ No

If so what kind? _____

3. Has the subject contacted new, special, or unusual substances (e.g., new laundry detergents, soap, personal care product, poison ivy, etc.)? □ Yes □ No

If so what kind? _____

4. Has the subject taken any other medication (over the counter, prescription, vitamins, and supplement)? □ Yes □ No

If so what kind? _____

5. Has the subject consumed unaccustomed, special or unusual foods? □ Yes □ No

If so what kind? _____

6. Does the subject have or had in the last few days any illness? □ Yes □ No

If so what kind? _____

7. Has the subject come into contact with any family or house members who are ill? □ Yes

□ No If so who and what? _____

8. Has the subject recently been near children who have a skin reaction, skin eruption, or rash (e.g. *Molluscum Contagiosum*)? □ Yes □ No

9. Has the subject had recent sun exposure? □ Yes □ No

10. For the current rash, have there been any systemic clinical signs? □ Yes □ No

If so what kind? _____

i. Anaphylaxis? □ Yes □ No
ii. Signs of hypotension? □ Yes □ No
iii. Signs of dyspnea? □ Yes □ No
iv. Fever, night sweats, chills? □ Yes □ No

11. For the current rash, has the subject needed subcutaneous epinephrine or other systemic catecholamine therapy? □ Yes □ No

If so what kind? _____

12. For the current rash, has the subject used any other medication, such as inhaled bronchodilators, antihistaminic medication, topical corticosteroid, and/or systemic corticosteroid? □ Yes □ No

List medication(s) and dose(s): _____
_____

13. Is the rash pruritic (itchy)? □ Yes □ No

8. APPENDIX 4 – Focused Skin Examination

Focused Skin Examination:
Key information should be summarized and entered on the Adverse Experience eCRF.

Primary Skin Lesions Description
Color: _____

General description:

_____
_____

Describe the distribution of skin reaction, skin eruption, or rash on the body:

_____
_____

Is skin reaction, skin eruption, or rash resolving or continuing to spread?

_____
_____

Any associated signs on physical examination?

_____