INDIANA UNIVERSITY
MELVIN AND BREN SIMON
COMPREHENSIVE CANCER CENTER

A Phase I/Ib, Open Label, Dose Finding Study to Evaluate Safety, Pharmacodynamics and Efficacy of Pembrolizumab (MK-3475) in Combination with Vorinostat in Patients with Advanced Prostate, Renal or Urothelial Cell Carcinoma

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PROTOCOL SIGNATURE PAGE

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VERSION DATE: 07April2021

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Instructions to the investigator: Please **SIGN** and **DATE** this signature page. **PRINT** your name and title, the name and location of the facility in which the study will be conducted, and the expected IRB approval date. Scan and email the completed form to Indiana University Simon Comprehensive Cancer Center and keep a record for your files.

_____ _____

Signature of Site Investigator Date

_____

Site Investigator Name (printed)

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Site Investigator Title

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Name of Facility

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Location of Facility (City and State)

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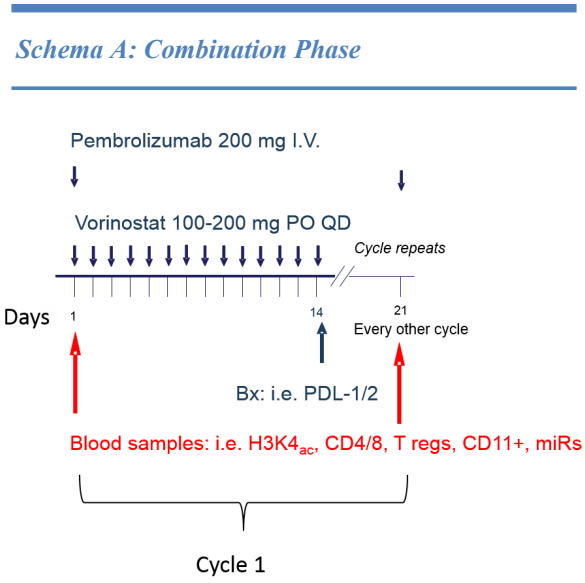
1.0 TRIAL SUMMARY

Abbreviated Title	Vorinostat and pembrolizumab in prostate, urothelial and renal cell carcinoma
Trial Phase	I/Ib
Clinical Indication	Metastatic disease
Trial Type	Interventional
Route of administration	IV and oral
Trial Blinding	N/A
Treatment Groups	Anti-PD1/PD-L1 naïve and anti-PD1/PD-L1 resistant tumors
Number of trial subjects	51-57
Estimated enrollment period	18 months
Estimated duration of trial	24 months
Duration of Participation	24 months

2.0 TRIAL DESIGN

2.1 Trial Design

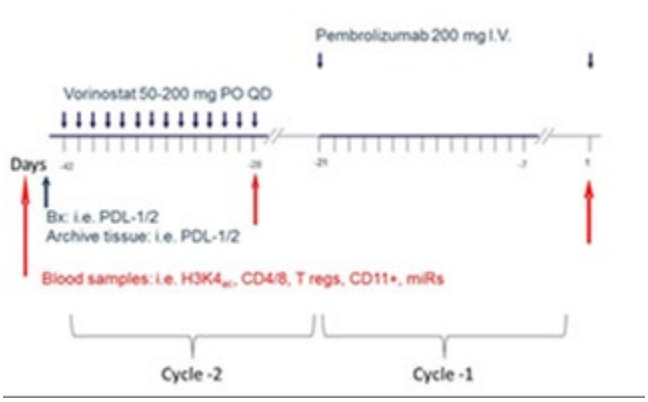
This is a Phase I/Ib, open-label, safety, and pharmacodynamics study of pembrolizumab in combination with vorinostat in patients with advanced prostate, renal or urothelial cell carcinoma. This clinical study will be composed of a Dose Finding Phase and an Expansion Phase. The Dose Finding Phase will estimate the Recommended Phase II Dose (RP2D) in patients with advanced renal and urothelial cell carcinoma patients. The Dose Finding Phase will lead to the identification of an Expansion Test Dose for pembrolizumab in combination with vorinostat. The Expansion Test Dose will be the Recommended Phase II Dose (RP2D) (i.e. the highest tested dose that is declared safe and tolerable by the Investigators and Sponsor). Patients will be treated with oral vorinostat every day for 14 days, and with pembrolizumab at the fixed dose of 200 mg IV. Each cycle is every 21 days. Two dose levels of vorinostat will be tested in 2-patient cohorts according to the 3 + 3 standard design (100 mg and 200 mg). 200 mg dose represents 50% of the recommended vorinostat dose as single agent.



For the Dose Finding Phase (Combination Phase, Schema A), the starting dose level of vorinostat will be 100 mg by mouth (PO) every day for 14 days, with 7 days break. The first dose level will have a minimum of 3 patients treated (unless the first 2 patients experience DLTs before the 3rd patient is enrolled).

DLTs are defined as Grade ≥ 3 hematological/non hematological toxicities attributable to vorinostat and/or pembrolizumab during the first 21 days of the combination treatment (days 1-21). If DLTs occur in 1 patient treated at the starting dose level a minimum of another 3 patients will be treated at this dose level. If a DLT occurs in more than 1 patient in the first 6 patients the study will be terminated. If a DLT occurs in ≤ 1/6 patients, 3 additional patients will be treated at the next dose level (level 2) with 200 mg vorinostat PO. If no DLTs occur at dose level 2, this dose level will be recommended for the expansion cohorts of the study. Patients who experience Grade ≥ 3 toxicity and recover to ≤ Grade 1 (or to pretreatment baseline level toxicity) may continue treatment at the next vorinostat lower level.

Schema B: Run-In Phase



Once the RP2D is identified, the Dose Expansion Phase will be opened. During the Dose Expansion Phase, the study will have a run-in phase with sequential single-agents (Schema B) and then the combination phase (Schema A). The run-in phase may be waived at the investigator's discretion. The reason for the run-in phase during dose expansion is to obtain data on the immunomodulatory effects of vorinostat separately from pembrolizumab. Forty-five patients with prior treatments will be enrolled in three expansion cohorts: 15 anti-PD1 naive renal and urothelial patients, 15 anti-PD1 resistant renal and urothelial patients (defined as patients with transient clinical response or without clinical response to prior immune-checkpoint inhibition), and 15 patients with androgen-sensitive or castration-resistant prostate cancer. The prostate cohort has been added in an amendment during the Dose Expansion Phase, and therefore, will not be part of the Dose Finding Phase.

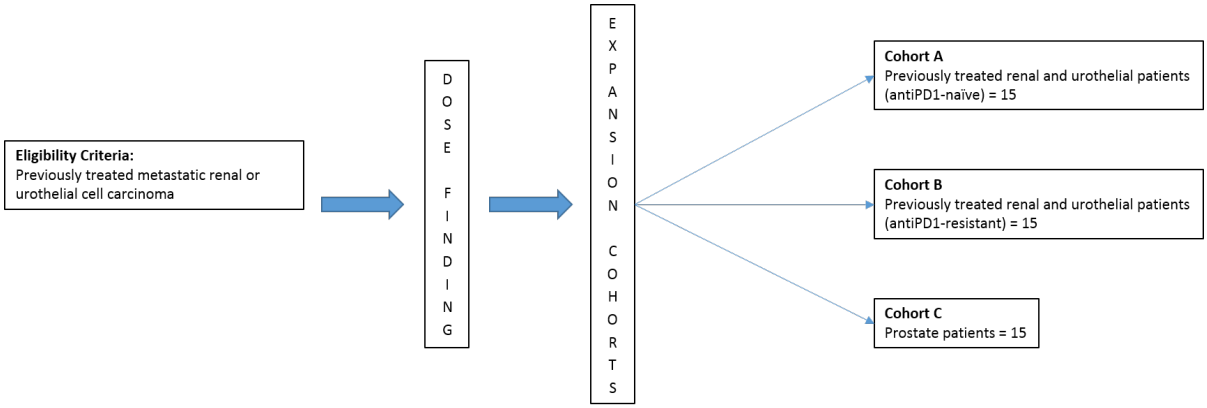
Anti-tumor activity will be assessed by radiological tumor assessments conducted at baseline, 12 weeks and every 6 weeks thereafter, using RECIST version 1.1 (see Section 14.3). RECIST 1.1 will be used for treatment decisions until first radiologic evidence of progressive disease (PD). Following the first evidence of radiologic PD, treatment decisions may be made by the adaption of RECIST 1.1, termed the immune-related response criteria (irRC) (see Section 14.6) to account for the tumor response patterns seen with pembrolizumab treatment (e.g. tumor flare).

1 Cycle = 3 weeks (21 days)

Dose Level	Pembrolizumab IV Q3W	Vorinostat PO QD x 14 days
1	200 mg	100 mg
2	200 mg	200 mg

The RP2D is the dose of pembrolizumab and vorinostat in combination chosen for further clinical development. Further experience in the Dose Expansion Cohort may result in a RP2D dose lower than the MTD.

2.2 Trial Diagram



3.0 OBJECTIVES

3.1 Primary Objective

To assess the early signals for anti-tumor activity (i.e. objective response rate, progression-free survival) of pembrolizumab in combination with vorinostat in patients with advanced prostate, renal or urothelial cell carcinoma.

3.2 Secondary Objectives

- To evaluate the overall safety profile of pembrolizumab in combination with vorinostat.
- To assess the safety and tolerability of pembrolizumab in combination with vorinostat in patients with advanced prostate, renal or urothelial cell carcinoma in order to select the recommended Phase 2 Dose (RP2D).

3.3 Correlative Objective

- To characterize immune cell subsets, and miRs in tumor and/or blood

4.0 BACKGROUND & RATIONALE

4.1 Background

Refer to the Investigator's Brochure (IB)/approved labeling for detailed background information on pembrolizumab and vorinostat (MK-3487).

4.1.1 Pharmaceutical and Therapeutic Background

Blocking the PD-1/PD-L1 interaction is a novel immunotherapeutic approach for the treatment of solid tumors including renal cell carcinoma (RCC). PD-1 inhibition has shown single-agent activity in clear cell RCC patients whose disease has progressed following VEGF pathway inhibitor therapy [1]. Recent data have also shown a significant activity of an anti PD-L1 antibody in urothelial cell carcinoma patients [2]. Though this new class of agents represents a very promising therapeutic strategy only a fraction of patients seems to achieve durable responses.

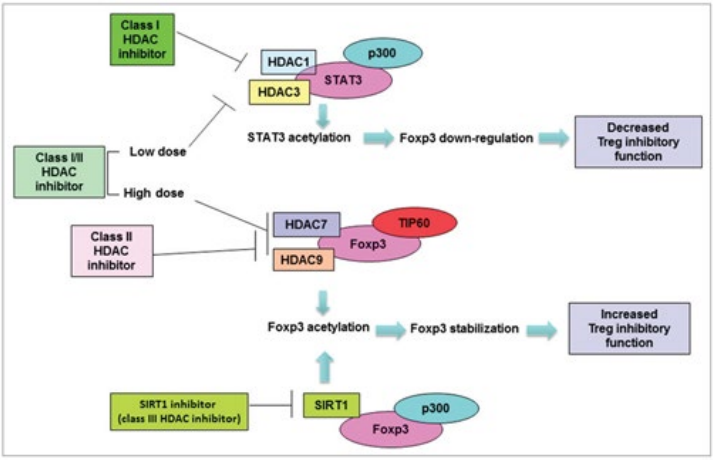


Figure 1. Modulation of Treg function with class-specific HDAC inhibitors. Class I HDAC inhibitors induce acetylation of STAT3 by inhibiting HDAC3 or HDAC1, downregulate Foxp3 gene expression and suppress Treg function. Class II HDAC inhibitor treatment induces Foxp3 hyperacetylation by targeting HDAC7 and HDAC 9, which leads to stabilization of Foxp3 protein and enhanced Treg function. SIRT 1 (Class III specific) inhibitor also induces hyperacetylation and stabilization of Foxp3 protein, and enhances the Treg function. A pan inhibitor may target Class I HDACs at a low dose and impair Treg function. At a higher dose, the pan inhibitor may target Class II HDAC and show a dominant Treg promoting effect[6]).

Pembrolizumab is a potent and highly selective humanized monoclonal antibody (mAb) of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Keytruda™ (pembrolizumab) has recently been approved in the United Stated for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilumumab and, if BRAF V600 mutation positive, a BRAF inhibitor.

Histone deacetylase (HDAC) inhibitors induce acetylation of several histone and non-histone proteins, which contributes to a wide spectrum of anti-tumor and immunomodulatory activities of this class of agents. Pan HDAC inhibitors have shown either immunosuppressive or immunopromoting properties through modulating cytokine expression, affecting macrophage and dendritic cells, or regulating costimulation molecules. HDAC inhibitors have been also shown to induce activation of major histocompatibility complex (MHC) class I and class II proteins, and co-stimulatory molecules CD40, CD80 and CD86. The results from the clinical trials with HDAC inhibitors in cutaneous T-cell lymphoma and large cell lymphoma patients that had lead the approval of vorinostat and romidepsin suggest that the antitumor activity these agents may be in part due to the modulation of the immune response. Our group has reported that the class I HDAC inhibitor entinostat suppresses regulatory T (Treg) cell function, enhances anti-tumor immune response and facilitates cytokine and vaccine immunotherapy in murine renal cell carcinoma and prostate cancer models, respectively [3,4]. This Treg suppression action does not seem to be through a depletion mechanism. On further analysis, we observed that entinostat suppresses Foxp3 gene expression in Treg cells and inhibits suppressive function of Treg cells. Entinostat acetylates STAT 3 leading to down regulation of Foxp3. Our preclinical data have shown the synergistic effect of entinostat in combination with high dose interleukin 2 in the RENCA model [4]. Based on these results, we have completed a CTEP-

sponsored phase I/II clinical trial with entinostat in combination with high dose interleukin 2 in patients with RCC (NCT01038778). The phase I results have been recently reported and suggest a biological and clinical activity of this combination [5]. Our preliminary data also suggest that inhibitors able to modify Class I HDACs (Class I specific and pan) decreased Foxp3 levels in Tregs in a dose-dependent manner, whereas class II specific HDAC inhibitors did not affect Foxp3 levels. This observation suggests that only class I HDAC inhibition results in Treg suppression. In addition, we observed that *in vivo* treatment with the pan HDAC inhibitor panobinostat showed opposite effects when applied at different doses: low dose inhibited Tregs suppressive function whereas high dose treatment promoted Treg function [6]. Panoninostat has much higher affinity for class I HDACs than for class II HDACs [7]. We hypothesize that pan HDAC inhibitors such as panobinostat and vorinostat primarily inhibit class I HDACs at low doses, which shows Treg suppressive effect similar to class I specific inhibitors. At a high dose, pan HDAC inhibitors saturate class I HDACs and targets class II, and the Treg-promoting effect resulting from class II HDACs inhibition becomes dominant.

4.2 Rationale

Novel strategies to enhance the antitumor activity of immune-checkpoint inhibitors are under development. This study will assess the immunomodulatory activity of vorinostat in patients receiving the PD1 inhibitor pembrolizumab. We have chosen two diseases (renal and urothelial cell carcinoma) that have been reported to respond to PD1/PD-L1 inhibition. We have also include a cohort of patients with prostate cancer as a recent report have shown activity of pembrolizumab after enzalutamide. However, as a proof of principle, we will include both hormone sensitive and castration resistant metastatic prostate cancer [8]. The schedule of vorinostat is based on our previous experience with this drug. We have completed a CTEP-sponsored phase I/II clinical trial with vorinostat in combination with bevacizumab in patients with pretreated RCC patients (NCT00324870). The dose of 200 mg PO (twice a day) BID 14 days on, 7 days off every 21 days was relatively well tolerated[9]. Based on the hypothesis that low dose pan HDAC inhibitors will have a suppressive function on Tregs but not on T effector cells, the starting dose of vorinostat will be 100 mg and will be escalated up to 200 mg only rather than the 400 mg dose approved for the treatment of cutaneous T cell lymphomas.

Based on our preclinical data, this study will test the following hypotheses:

1. Class I HDAC inhibition by either selective Class I HDAC or low dose pan HDAC inhibitors may decrease Tregs and MDSCs without affecting T effector cells

2. Vorinostat may enhance the anti-tumor activity of immune-check point inhibitors by suppressing inhibitory cells and inducing PDL-1/2 expression.

3. Vorinostat may re-sensitize patient previously treated with immune-check point inhibitors.

4.2.1 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 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.

Pharmacokinetic (PK) data analysis of pembrolizumab administered Q2W and Q3W showed slow systemic clearance, limited volume of distribution, and a long half-life (refer to Investigator Brochure). Pharmacodynamic (PD) data (IL-2 release assay) suggested that peripheral target engagement is durable (>21 days). This early PK and PD 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 non-small-cell lung carcinoma (NSCLC) and melanoma indications. Therefore, there are no anticipated changes in exposure between different indication settings.

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

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

The choice of the starting dose of vorinostat (100 mg) is based on the preclinical data suggesting that low dose of pan HDAC inhibitors may have already positive immunomodulatory activity (see 4.1.1).

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Subject Inclusion Criteria

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

1. Have one of the following diagnoses/conditions:

    a. Renal cell carcinoma - previously treated and progressive disease, locally advanced or metastatic

    b. Urothelial cell carcinoma - previously treated and progressive disease, locally advanced or metastatic

    c. Prostate cell carcinoma - progressive disease, locally advanced or metastatic disease (enrolling only at IUSCC and its affiliates). Patients with hormone-sensitive disease where ADT in combination with either docetaxel or abiraterone is indicated will not be eligible (i.e. patients with high burden disease).

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

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

4. Have measurable disease based on RECIST 1.1 (Section 14.3) for patients with solid malignancies or evaluable disease as assessed by bone scan and/or PET scan. Patients with advanced or metastatic prostate cancer can have either androgen-sensitive or castration-resistant disease.

5. Have a performance status of 0-2 on the ECOG Performance Scale (Section 14.1).

6. Demonstrate adequate organ function as defined in Table 1.

Table 1: Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1,500 /mcL
Platelets	≥100,000 / mcL
Hemoglobin	≥9 g/dL or ≥5.6 mmol/L without transfusion or EPO dependency (within 7 days of assessment)
Renal	
Serum creatinine **OR** Measured or calculated[a] creatinine clearance	≤1.5 X upper limit of normal (ULN) **OR**

(GFR can also be used in place of creatinine or CrCl)	≥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
Albumin	≥2.5 mg/dL
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT)	≤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
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
[a]Creatinine clearance should be calculated per institutional standard.	

7. Female subject of childbearing potential (see appendix 14.6) should have a negative urine or serum pregnancy test within 72 hours prior to receiving the first dose of study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

8. Subjects of childbearing potential should be willing to use 2 methods of contraception for the course of the study through 120 days after the last dose of study medication (reference Section 5.5.2). Acceptable methods of birth control include: abstinence, partner with previous vasectomy, placement of an intrauterine device (IUD), condom with spermicidal foam/gel/film/cream/suppository, diaphragm or cervical vault cap, or hormonal birth control (pills or injections). NOTE: Females are considered of childbearing potential unless they are surgically sterile (they have undergone a hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or they are postmenopausal (a woman who is ≥ 45 years of age and has not had menses for greater than 1 year).

9. Male subjects without a previous vasectomy should agree to use an adequate method of contraception (i.e. abstinence, condom with spermicidal foam/gel/film/cream) starting with the first dose of study therapy through 120 days after the last dose of study therapy.

10. Subjects with urothelial carcinoma must have received a prior platinum-based regimen in the metastatic setting or have signed consent for this study within 12 months of receiving a platinum-based regimen in the perioperative setting (neoadjuvant or adjuvant).

11. Subjects with a history of diabetes mellitus must have HgbA1c level of < 8.5% upon study entry.

5.1.2 Subject Exclusion Criteria

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

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

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.

3. Has active TB (Bacillus Tuberculosis)

4. Hypersensitivity to pembrolizumab or any of its excipients.

5. Has had a prior anti-cancer monoclonal antibody (mAb) within 4 weeks prior to Cycle 1 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.

6. Has had prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to Cycle 1 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.

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

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

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

10. Has known history of, or any evidence of active, non-infectious pneumonitis.

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

15. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent (only during Dose Expansion Phase for Cohort A).

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 of planned start of study therapy.

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	Q3W	IV infusion	Day 1 of each 3 week cycle	Experimental
Vorinostat	100-200 mg	QD	oral	Day 1-14 of each 3 week cycle	Experimental

Trial treatment should begin as close as possible to the date on which treatment is allocated/assigned.

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 & Rationale.

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

5.2.1.2 Dose Administration

Treatment cycles consist of daily oral dosing of vorinostat (Days 1 through 14) and intravenous dosing of pembrolizumab (Day 1, Cycle 1). The two-drug regimen will be given every 3 weeks. The starting dose of vorinostat will be 100 mg orally QD per day for Days 1 through 14. The dose of pembrolizumab will be 200 mg IV on Day 1, every 21 days.

5.2.1.3 Definition of Dose-Limiting Toxicity (DLT)

DLTs include any Grade 3-5 toxicity related to vorinostat or pembrolizumab during the combination phase only (Cycle 1) (except for a ≥ Grade 3 decrease in lymphocytes). Grade 3 nausea or vomiting should be considered a DLT only if unresponsive to therapy and ≥ 72 hours in duration. Patients must have taken at least 4 of the 14 doses of vorinostat to be considered evaluable for DLT determination. Patients who do not complete the first cycle of combination therapy during the dose finding phase will be replaced. Patients who do not receive at least 75% of the expected dose of vorinostat due to toxicity are considered to have DLT. Delay in treatment due to a toxicity greater than 2 weeks is also considered a DLT. ALT>3xULN + Total bilirubin >2xULN will be a DLT which results in permanent drug discontinuation.

3 patients will be enrolled at dose level 1:

- If 1 DLT occurs in the first 3 patients, expand dose level 1 to 6 patients.
- If 0-1 DLT occur in 6 patients, expand to dose level 2.
- If 1 DLT occurs in the first 3 patients, expand dose level 2 to 6 patients.
- If ≥ 2 DLTs occur in the 3-6 patient cohort at dose level 2, the lower dose level will be considered the MDT.
- If ≥ 2 DLTs occur in the 3-6 patient cohort at dose level 1, the study will be terminated.

5.2.1.4 Supportive Care Guidelines

Note: there is an overlap in potential toxicity related to diarrhea.

If the patient has diarrhea (loose stool) = Grade 2, follow the supportive care guidelines for Vorinostat below. If the patient has diarrhea (loose stool) ≥ Grade 3, follow the supportive care guidelines for Vorinostat below.

If a patient has colitis (diarrhea with abdominal pain, mucus or blood in stool) ≥ Grade 2, follow the supportive care guidelines for Pembrolizumab below.

Vorinostat: Because vorinostat's dose limiting toxicities are anorexia, dehydration, diarrhea, and fatigue, patients should maintain adequate fluid and food intake. Patients will be encouraged to seek a nutritional consult, if necessary.

Treat diarrhea promptly with appropriate supportive care, including loperamide. Instruct patients to begin taking loperamide at the first signs of:

- Poorly formed or loose stool
- Occurrence of more bowel movements than usual in one day, or
- Unusually high volume of stool.

Loperamide should be taken in the following manner: 4 mg at first onset of diarrhea, then 2 mg after each unformed stool. Daily dose should not exceed 16 mg/day. Loperamide should not be taken prophylactically. Advise patients to drink plenty of clear fluids to help prevent dehydration caused by diarrhea. Avoid loperamide if there is the presence of blood or mucus in the stool or if diarrhea is accompanied by fever. If grade 3 or 4 diarrhea develops on loperamide, discontinue further treatment with vorinostat.

Pembrolizumab: Supportive care guidelines for pembrolizumab can be found in Appendix 14.5.

5.2.1.5 Duration of Therapy

Patients may continue on therapy until one of the following criteria applies:

- Disease progression (with the exception of pseudoprogression as described in Section 5.9),
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s),
- Patient decides to withdraw from the study, or
- General or specific changes in the patient's condition that renders the patient unacceptable for further treatment in the judgment of the investigator.

5.2.1.6 Dose Modifications

Vorinostat should be held when ≥ Grade 3 to 4 drug-related adverse experiences occur. After resolution of these adverse experiences to Grade 1 or less (or to pretreatment baseline level of toxicity) treatment with vorinostat may continue at the next lower dose (see 2.1). Once the dose has been reduced, patients must remain at the reduced dose for the remainder of the study. Patients may have their dose reduced once before being removed from the trial. Patients may only have their dose reduced to dose level 1. If grade 3 or 4 diarrhea develops despite supportive care, patients will discontinue further treatment with vorinostat.

Vorinostat in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

Please see tables below for a list of adverse events experienced by patients who have been treated with vorinostat.

Experiences by Preferred Terms experienced by ≥10% of All Patients
Overall Population - Vorinostat Patients

	Total							
	All Events				Drug-Related Events			
	All Grades		Grades 3-5		All Grades		Grades 3-5	
	n	(%)	n	(%)	n	(%)	n	(%)
Patients in population	1,744		1,744		1,744		1,744	
with one or more adverse events	1,701	(97.5)	1,291	(74.0)	1,561	(89.5)	957	(54.9)
with no adverse events	43	(2.5)	453	(26.0)	183	(10.5)	787	(45.1)
Nausea	995	(57.1)	100	(5.7)	895	(51.3)	86	(4.9)
Diarrhoea	892	(51.1)	126	(7.2)	759	(43.5)	116	(6.7)
Fatigue	821	(47.1)	221	(12.7)	700	(40.1)	188	(10.8)
Vomiting	661	(37.9)	63	(3.6)	566	(32.5)	56	(3.2)
Thrombocytopenia	630	(36.1)	443	(25.4)	537	(30.8)	372	(21.3)
Anaemia	489	(28.0)	210	(12.0)	296	(17.0)	101	(5.8)
Decreased appetite	455	(26.1)	47	(2.7)	373	(21.4)	39	(2.2)
Constipation	448	(25.7)	25	(1.4)	230	(13.2)	12	(0.7)
Neutropenia	396	(22.7)	306	(17.5)	311	(17.8)	232	(13.3)
Dyspnoea	335	(19.2)	80	(4.6)	97	(5.6)	11	(0.6)
Pyrexia	331	(19.0)	23	(1.3)	116	(6.7)	6	(0.3)
Cough	311	(17.8)	12	(0.7)	46	(2.6)	2	(0.1)
Weight decreased	284	(16.3)	14	(0.8)	213	(12.2)	12	(0.7)
Asthenia	248	(14.2)	77	(4.4)	170	(9.7)	62	(3.6)
Blood creatinine increased	227	(13.0)	6	(0.3)	170	(9.7)	3	(0.2)

Experiences by Preferred Terms experienced by ≥10% of All Patients
Overall Population - Vorinostat Patients (Cont.)

	Total							
	All Events				Drug-Related Events			
	All Grades		Grades 3-5		All Grades		Grades 3-5	
	n	(%)	n	(%)	n	(%)	n	(%)
Anorexia	226	(13.0)	23	(1.3)	197	(11.3)	21	(1.2)
Hyperglycaemia	223	(12.8)	42	(2.4)	139	(8.0)	21	(1.2)
Leukopenia	211	(12.1)	112	(6.4)	170	(9.7)	75	(4.3)
Headache	210	(12.0)	10	(0.6)	88	(5.0)	6	(0.3)
Dizziness	207	(11.9)	14	(0.8)	108	(6.2)	8	(0.5)
Dysgeusia	203	(11.6)	2	(0.1)	186	(10.7)	2	(0.1)
Alopecia	188	(10.8)	11	(0.6)	139	(8.0)	8	(0.5)
Abdominal pain	184	(10.6)	22	(1.3)	95	(5.4)	6	(0.3)
Hypokalaemia	179	(10.3)	67	(3.8)	90	(5.2)	31	(1.8)
Back pain	177	(10.1)	24	(1.4)	19	(1.1)	2	(0.1)

Every patient is counted a single time for each applicable specific adverse event. A patient with multiple adverse events within a system organ class is counted a single time for that system organ class.

A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns is greater than or equal to the percent incidence specified in the report title, after rounding.

Only the highest reported grade of a given adverse event is counted for the individual patient.

Pembrolizumab:

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

Attribution of Toxicity:

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

Holding Study Interventions:

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

Restarting Study Interventions:

Participants may not have any dose modifications (no change in dose or schedule) of pembrolizumab in this study, as described in Table 3.

1. If the toxicity does not resolve or the criteria for resuming treatment are not met, the participant must be discontinued from all study interventions.

2. If the toxicities do resolve and conditions are aligned with what is defined in Table 3, the combination of vorinostat and pembrolizumab may be restarted at the discretion of the investigator. In these cases where the toxicity is attributed to the combination or to vorinostat alone, re-initiation of pembrolizumab as a monotherapy may be considered at the principal investigator's discretion.

Pembrolizumab may be interrupted for situations other than treatment-related AEs such as medical / surgical events and/or unforeseen circumstances not related to study intervention. However, intervention is to be restarted within 3 weeks of the originally scheduled dose and within 42 days of the previously administered dose, unless otherwise discussed with the Sponsor. The reason for study intervention interruption is to be documented in the patient's study record.

Table 3: Dose modification and toxicity management guidelines for immune-related AEs associated with pembrolizumab monotherapy and IO Combinations

General instructions:

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

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper • Add prophylactic antibiotics for opportunistic infections	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment
	Recurrent Grade 2, Grade 3 or 4	Permanently discontinue		

Diarrhea/Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus) • Participants with ⩾Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion
	Recurrent Grade 3 or Grade 4	Permanently discontinue		
AST or ALT Elevation or Increased Bilirubin	Grade 2 [a]	Withhold	• Administer corticosteroids (initial dose of 0.5 to 1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable)
	Grade 3 [b] or 4 [c]	Permanently discontinue	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	
T1DM or Hyperglycemia	New onset T1DM or Grade 3 or 4 hyperglycemia associated	Withhold [d]	• Initiate insulin replacement therapy for participants with T1DM	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes

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

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

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

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

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

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

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

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

[e] Events that require discontinuation include, but are not limited to: encephalitis and other clinically important irAEs.

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

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

Table 4 Pembrolizumab Infusion Reaction Dose modification and Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g. from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until	Participant may be premedicated 1.5h (± 30 minutes) prior to infusion of study intervention with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of analgesic).

	symptoms resolve and the participant should be premedicated for the next scheduled dose. **Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug intervention**	
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: Epinephrine** IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Oxygen Pressors Corticosteroids Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. **Participant is permanently discontinued from further study drug intervention.**	No subsequent dosing
Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the Common Terminology Criteria for Adverse Events v5.0 (CTCAE) at http://ctep.cancer.gov		

5.2.1.6 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 Schedule of Assessments (Section 6.0). Trial treatment may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons.

All trial treatments will be administered on an outpatient basis.

Pembrolizumab 200 mg will be administered as a 30 minute IV infusion every 3 weeks. 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 package insert contains specific instructions for the preparation of the pembrolizumab infusion fluid and administration of infusion solution.

Patients should store vorinostat capsules at room temperature, 15 to 30 ºC (59 to 86 ºF). Do not store above 30^0C. Avoid exposure to excessive moisture. Vorinostat capsules must be administered whole. Administer doses of vorinostat with food if possible. Vorinostat capsule should be administered according to the package insert.

5.2.2 Trial Blinding/Masking

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

5.3 Concomitant Medications/Vaccinations (allowed & prohibited)

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

5.3.1 Acceptable Concomitant Medications

All treatments that the investigator considers necessary for a subject’s welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. 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 written informed consent and 30 days after the treatment discontinuation should be recorded. Concomitant medications

administered after 30 days after treatment discontinuation should be recorded for SAEs and ECIs as defined in Section 7.2.

5.3.2 Prohibited Concomitant Medications

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

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab and vorinostat
- Radiation therapy
    - Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed at the investigator's discretion with written Sponsor approval.
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, Bacillus Calmette-Guérin, and typhoid vaccine.
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.

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

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

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

5.4 Rescue Medications & Supportive Care

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of adverse events with potential immunologic etiology for pembrolizumab are outlined in section 5.2.1.6 of the protocol and in section 6.4.1 of the Investigator's Brochure. Where appropriate, these guidelines include the use of oral or intravenous treatment with corticosteroids as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might

require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab.

Note: if after the evaluation the event is determined not to be related, the investigator is instructed to follow the Investigator's Brochure but does not need to follow the treatment guidance (as outlined in the Investigator's Brochure). Refer to Section 5.2.1.6 for dose modifications.

It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event. Suggested conditional procedures, as appropriate, can be found in the Investigator's Brochure.

5.5 Diet/Activity/Other Considerations

5.5.1 Diet

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

5.5.2 Contraception

Pembrolizumab and vorinostat may have adverse effects on a fetus in utero. Furthermore, it is not known if pembrolizumab or vorinostat have transient adverse effects on the composition of sperm. Non-pregnant, non-breast-feeding women may be enrolled if they are willing to use 2 methods of birth control or are considered highly unlikely to conceive. Highly unlikely to conceive is defined as 1) surgically sterilized (they have undergone a hysterectomy, bilateral tubal ligation, or bilateral oophorectomy), or 2) postmenopausal (a woman who is ≥45 years of age and has not had menses for greater than 1 year will be considered postmenopausal), or 3) not heterosexually active for the duration of the study. Acceptable methods of birth control include: abstinence, partner with previous vasectomy, placement of an intrauterine device (IUD), condom with spermicidal foam/gel/film/cream/suppository, diaphragm or cervical vault cap, or hormonal birth control (pills or injections). Subjects should start using birth control from written informed consent throughout the study period up to 120 days after the last dose of study therapy.

Male subjects without a previous vasectomy should agree to use an adequate method of contraception (i.e. abstinence, condom with spermicidal foam/gel/film/cream) starting with the first dose of study therapy through 120 days after the last dose of study therapy.

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 they must adhere to the contraception requirement (described above) for the duration of the study and during the follow-up period defined in section 7.2.3-Pregnancy and Lactation. 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.

5.5.3 Use in Pregnancy

If a subject inadvertently becomes pregnant while on treatment with pembrolizumab and/or vorinostat, the subject will immediately be removed from the study. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the Sponsor and to Merck without delay and within 24 hours to the Sponsor and within 2 working days to Merck if the outcome is a serious adverse experience (e.g. death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn).

The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor. 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 7.2.3.

5.5.4 Use in Nursing Women

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

5.6 Subject Withdrawal/Discontinuation Criteria

Subjects may withdraw consent at any time for any reason or be removed 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. If a subject withdraws from the study, they will no longer receive study intervention or be followed at scheduled protocol visits. Specific details regarding discontinuation or withdrawal are provided in Section 7.1.4.1.

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 (with the exception of pseudoprogression as described in Section 5.9)
- Any progression or recurrence of any malignancy, or any occurrence of another malignancy that requires active treatment
- Unacceptable adverse experiences as described in Section 5.2.1.7
- Intercurrent illness that prevents further administration of treatment
- Investigator's decision to withdraw the subject
- The subject has a confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements
- The subject is lost to follow-up
- Completed 24 months of uninterrupted treatment with pembrolizumab or 35 administrations of study medication, whichever is later.

Note: 24 months of study medication is calculated from the date of first dose. Subjects who stop pembrolizumab after 24 months may be eligible for up to one year of additional study treatment if they progress after stopping study treatment provided they meet the requirements detailed in Section 7.1.6.4

- Administrative reasons

The End of Treatment and Follow-up visit procedures are listed in Section 6 (Schedule of Assessments) and Section 7.1.6 (Follow-up 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). Subjects who discontinue for reasons other than progressive disease will have post-treatment follow-up for disease status until disease progression, initiating a non-study cancer treatment, withdrawing consent or becoming lost to follow-up. After documented disease progression, each subject will be followed by telephone for overall survival until death, withdrawal of consent, or the end of the study, whichever occurs first.

5.7 Discontinuation of Study Therapy after CR

Discontinuation of treatment may be considered for subjects who have attained a confirmed CR that have been treated for at least 24 weeks with combination vorinostat and pembrolizumab and had at least two treatments with vorinostat and pembrolizumab beyond the date when the initial CR was declared. Subjects who then experience radiographic disease progression may be eligible for up to one year of additional treatment with vorinostat and pembrolizumab via the Retreatment Phase at the discretion of the investigator if no cancer treatment was administered since the last dose of vorinostat and pembrolizumab, the subject meets the safety parameters listed in the Inclusion/Exclusion criteria, and the trial is open. Subjects will resume therapy at the same dose and schedule at the time of initial discontinuation. Additional details are provided in Section 7.1.6.4.

5.8 Subject Replacement Strategy

Patients who do not complete the first cycle of combination therapy during the dose finding phase will be replaced. Patients who cannot complete Cycle 1 of the expansion phase for reasons unrelated to the study drug will also be replaced.

5.9 Pseudoprogression

For a clinically stable subject with first radiologic evidence of progressive disease (PD), it is at the discretion of the site investigator to continue treating the subject with pembrolizumab until PD is confirmed at least 6 weeks from the date of the first tumor imaging suggesting PD. If radiologic PD is confirmed by the subsequent tumor imaging the subject should be discontinued from treatment unless, in the opinion of the investigator, the subject is achieving a clinically meaningful benefit.

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 SCHEDULE OF ASSESSMENTS

Trial Period:	**Screening Phase**	**Run-in Phase[13]**		**Combination Phase**									**End of Treatment**	**Post-Treatment**		
Treatment Cycle	Screening[1] (Visit 1)	-2	-1	1	1 D 14	2	3	4	To be repeated beyond 8 cycles 5	 6	 7	 8	Discontinuation	Safety Follow-up[2]	Follow-up Visits[3]	Survival Follow-up
Scheduling Window (Days):	-28 days to start of first cycle	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	30 days post discon ± 3	Per institutional guidelines	Every 6 months ± 30
Administrative Procedures																
Informed Consent	x															
Inclusion/Exclusion Criteria	x															
Demographics and Medical History	x															
Registration	x															
Prior and Concomitant Medication Review	x															
Trial Treatment Administration		x	x	x	x	x	x	x	x	x	x	x				
Post-study anticancer therapy status													x	x	x	x
Survival Status																x
Clinical Procedures/Assessments																
Review Adverse Events			x	x		x	x	x	x	x	x	x	x	x		
Full Physical Examination[4]	x	x	x	x		x	x	x	x	x	x	x	x			
Drug Compliance Review			x		x	x	x	x	x	x	x	x	x			
Vital Signs, Weight and Height (Screening Only)	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			
Laboratory Procedures/Assessments[9]																

Trial Period:	**Screening Phase**	**Run-in Phase[13]**		**Combination Phase**									**End of Treatment**	**Post-Treatment**		
Treatment Cycle	Screening[1] (Visit 1)	-2	-1	1	1 D 14	2	3	4	To be repeated beyond 8 cycles 5	 6	 7	 8	Discontinuation	Safety Follow-up[2]	Follow-up Visits[3]	Survival Follow-up
Scheduling Window (Days):	-28 days to start of first cycle	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	30 days post discon ± 3	Per institutional guidelines	Every 6 months ± 30
Pregnancy Test – Urine or Serum β-HCG	x [5]			x [5]									x [5]			
PT/INR and aPTT	x															
CBC with Differential	x	x	x	x	x	x	x	x	x	x	x	x	x			
Comprehensive Serum Chemistry Panel	x	x	x	x		x	x	x	x	x	x	x	x			
Urinalysis	x		x			x		x		x		x	x			
T3, FT4 and TSH	x		x			x		x		x		x	x			
HgbA1c[11]	x	x	x	x		x	x	x	x	x	x	x				
Prostate Specific Antigen Test				x			x		x		x		x			
Efficacy Measurements																
Tumor Imaging – CT[16]	x						x[13]			x[16]			x[12]		x [6]	
Tumor Imaging - Bone Scan	x						x[12, 13]			x[12,16]			x[12]			
Tumor Imaging - ^{68}Ga-PSMA-11 PET Scan[17]	x							x[17]								
Tumor Biopsies/Archival Tissue Collection/Correlative Studies Blood																
Archival (when available), Newly Obtained Tissue Collection (optional) [7]	x				x[15]											
Correlative Studies Blood Collection	x	X[8]		x		x		x		x		x	x [10]			

Footnotes:

[1] Procedures completed prior to consenting that are a part of a subject's standard of care may be used if they fall within the 28 day window to start treatment. Screening procedures completed 7 days of C1D1 do not need to be repeated.

[2] If the subject discontinues treatment due to disease progression, a phone call to the patient can serve as the Safety Follow-up Visit if the End of Treatment Visit was done. If a subject initiates a new anti-cancer therapy within 30 days after the treatment discontinuation, 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.

[3] Applies to subjects who discontinue trial treatment for a reason other than disease progression. Subjects should be assessed per institutional guidelines 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.

[4] Full physical exams may also be done by the investigator or qualified designee throughout participation in the trial as clinically indicated.

[5] Only if clinically indicated and must be completed ≤ 7 days prior to the first dose of study medication

[6] It is recommended that after 1 year, imaging should be done every 6 months ± 2 weeks; however, institutional guidelines and investigator discretion may vary.

[7] Whenever possible, archival tissue from a tumor lesion will be obtained at screening. However, patients will be given the option to consent to a biopsy during the screening phase in case archival tissue cannot be retrieved and a second biopsy on Cycle 1 Day 14 (- 3 days). Missed tissue collection will not be considered a protocol deviation for the purposes of this study, as tissue collection is an exploratory objective for this study.

[8] Run-in Phase, Cycle -2 Days 1 and 14

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

[10] When patients are taken off treatment and at the time of disease progression blood for correlative markers will be also obtained.

[11] HcbA1c only required for patients with diabetes mellitus at time of study entry.

[12] Only as clinically indicated (Cohort A and B). Standard of care after initial ^{68}Ga-PSMA-11 PET (Cohort C)

[13] Imaging will be done prior to dosing on C3D1.

[14] The run-in phase will only be done during the Dose Expansion Phase and may be waived at the investigator's discretion.

[15] Window for second biopsy is -3 days not +/- 3 days as is the case for other procedures at this time point. Biopsy should occur approximately 2 hours following the most recent dose of vorinostat on cycle 1 day 14. To ensure that these samples are obtained at the correct time, patients are urged to take their vorinostat dose in the clinic on the day of on-treatment sample collection.

[16] Imaging will be done every 3 cycles beginning cycle 6 throughout treatment.

[17] Applicable to a subset of patients in Cohort C (prostate cancer) only, as determined by the Principal Investigator. The Ga-PSMA-11 PET scan should be completed at 12 weeks (C4D1)

7.0 TRIAL PROCEDURES

7.1 Trial Procedures

The Schedule of Assessments -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.

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's approval 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 if the new information would affect the subject's willingness to continue participation in the study as determined by the IRB.

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 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 during the screening period. 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

During the screening period, 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 written informed consent. 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 events of clinical interest (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 treatment discontinuation. If a subject initiates a new anti-cancer therapy within 30 days after treatment discontinuation, 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 Screening and Registration Number

Subjects will be assigned a screening and registration number in sequential order by the Coordinating Center's study coordinator, or for participating sites, the Multicenter Network Administrator, or designee. Additional details of this process can be found in the Study Procedures Manual.

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

Subjects will be given a drug diary (Section 14.4) to record doses of vorinostat and any adverse events he or she may experience. Drug diaries will be collected at the start of the next cycle, or at the time of the next clinic visit, whichever is sooner. Any discrepancies in drug accountability will be clarified with the subject.

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 Schedule of Assessments and more frequently if clinically indicated. Adverse events will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE Version 4.0 (reference Section 14.2). 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 (termed immune-related adverse events, or irAEs); see the separate package insert regarding the identification, evaluation and management of potential irAEs. Detailed information regarding ECIs can be found in Section 14.5.

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. Clinically significant abnormal findings should be recorded as medical history. Full physical exams may also be done by the investigator or qualified designee throughout participation in the trial as clinically indicated and as specified in the Schedule of Assessments (section 6.0.) After the first dose of study intervention, new clinically significant abnormal findings should be recorded as AEs.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

7.1.2.3 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 Schedule of Assessments (Section 6.0). Vital signs should include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at screening only.

7.1.2.4 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG status (see Section 14.1) at screening, prior to the administration of each dose of trial treatment and discontinuation of trial treatment as specified in the Schedule of Assessments.

7.1.2.5 Tumor Imaging and Assessment of Disease

Imaging studies (CT and bone scan) will be performed at baseline, before Cycle 3, every 3 cycles thereafter and at treatment discontinuation as described in Section 7.1.4.1 below. CT modalities should be done according to standard of care for the patient's disease. Bone scans should be done at baseline and then only as clinically indicated.

Patients in Cohort C (prostate) will have two PET scans using ^{68}Ga-PSMA-11: once at baseline and then at 12 weeks (Cycle 4) Not all patients in Cohort C will have the additional PET scans. This determination will be made by the Principal Investigator.

Participant eligibility will be determined using local assessment (Investigator assessment) based on RECIST 1.1. In addition, images (including via other modalities) that are obtained at an unscheduled time point to determine disease progression, as well as imaging obtained for other reasons, but which demonstrate radiologic progression, should also be used to determine progression.

When the Investigator identifies radiographic progression per RECIST 1.1, efforts should be made to verify radiologic PD. Treatment should continue until PD has been verified. Regardless of whether PD is verified, if the Investigator considers the participant has progressed, but elects to implement irRC, the Investigator will assess for confirmation of progression by irRC at subsequent time points.

7.1.2.6 Tumor Tissue Collection and Correlative Studies Blood Sampling

7.1.2.6.1 Pharmacodynamic Analysis

All biopsies on this trial are optional for patients. Whenever possible, archival tissue from a tumor lesion will be obtained at screening. If archived tissue is not available, patients will be given the option to consent to a biopsy during the screening phase. Patients will also be given the option to consent to a biopsy on Day 14 of Cycle 1 (window -3 days). The treatment biopsy should occur approximately 2 hours following the most recent dose of vorinostat on cycle 1 day 14. To ensure that these samples are obtained at the correct time, patients are urged to take their vorinostat dose in the clinic on the day of on-treatment sample collection.

Biopsy for tumor tissue collection will only be done on patients who have accessible tumor per institutional guidelines. Missed tissue collection will not be considered a protocol deviation for the purposes of this study, as tissue collection is an exploratory objective for this study.

Biomarker studies on tumor and blood biospecimens will be carried out to help understand the mechanism of action of the pembrolizumab and vorinostat combination. The run-in phase will help to assess the effect of single agents on the potential biomarkers. Results from these correlative studies will help in the identification of potential biomarkers of response to the pembrolizumab plus vorinostat combination, ultimately leading to the development of a patient selection strategy for further clinical investigation. As such, collection of tumor and blood biospecimens at baseline and on study will be of great importance.

The pharmacodynamics of vorinostat and pembrolizumab will be evaluated. Correlative studies will include assessment of immune effects Tregs, MDSCs and other immune cells at defined time points per the study calendar (i.e., baseline, Run-in Phase Cycle -2 Days 1 and 14 [Dose Expansion Phase only], Cycle 1 Day 1 before dosing, Cycle 2 Day 1 before dosing, every other cycle day 1 before dosing thereafter, and at treatment discontinuation).

Imaging studies (CT and bone scan) will be performed at baseline, before Cycle 3, every 3 cycles thereafter and at treatment discontinuation.

Relationships between vorinostat exposure and pharmacodynamic effects (e.g. histone acetylation in peripheral blood mononuclear cells (PBMNCs) and changes in T cell subset population) will be characterized. Samples will be processed, PBMNCs isolated and histone acetylation status determined. Blood samples will be analyzed for immune cell sub populations. CD4+, CD4+/Foxp3, CD8+ cells, NK cells will be quantitated by FACS analysis. Foxp3 gene expression will be evaluated by quantitative RTPCR

Correlative studies on blood samples:

- CD45 cells
- Effector CD4 T cells
- Effector CD8 T cells
- FoxP3+ CD4+ Regulatory T cells (Tregs)
- CD11b+ CD14+ HLA-DR low/neg MDSCs
- Circulating microRNAs
- Chemokines profile (i.e. IL-8, HFG, ostepontin, etc.)

Correlative studies on tumor samples

- T effector cells
- Tregs
- MDSCs
- M1/M2 macrophages

Please refer to the Study Procedures Manual for Sample Collection and Processing and shipping instructions.

7.1.2.6.2 Tumor Samples

Formalin-Fixed Paraffin-Embedded Tissue: Archival tissue samples may be obtained from any time prior to drug dosing from either the original diagnosis or from any subsequent biopsy done prior to start of first drug treatment. Paraffin blocks are preferred, but if unavailable, five (5) 4 micron sections and two (2) to six (6) 10 micron sections from the same tumor block will be requested.

Fresh tumor samples: Pretreatment and On Treatment tumor biopsy samples will be collected from patients who consent and who have accessible tumor per institutional procedures. The biopsy sample will be split into **two** portions: one (1) portion will be placed in RNA*later*™ and one (1) portion will be placed in 10% formalin solution.

The On Treatment samples will be collected ~2 hours following the most recent dose of vorinostat on cycle 1 day 14 (-3 days). To ensure that these samples are obtained at the correct time, patients are urged to take their vorinostat dose in the clinic on the day of on-treatment sample collection. The time of the vorinostat dose and sample collection must be recorded.

Please refer the Study Procedures Manual for additional processing and shipping instructions.

7.1.3 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments for hematology, chemistry, urinalysis, and others are specified in Table 5. The Schedule of Assessments - Section 6.0 summarizes the laboratory procedures to be performed at each visit.

Laboratory tests for screening or entry into the Retreatment Phase should be performed within 10 days prior to the first dose of treatment. After Cycle -2, pre-dose laboratory procedures can be conducted up to 72 hours prior to dosing. Results must be reviewed by the investigator or qualified designee and found to be acceptable prior to each dose of trial treatment.

Table 5: Laboratory Tests

Hematology	**Chemistry**	**Urinalysis**	**Other**
Hematocrit	Albumin	Blood	Serum β-human chorionic gonadotropin†
Hemoglobin	Alkaline phosphatase	Glucose	(β-hCG)†
Platelet count	Alanine aminotransferase (ALT)	Protein	PT (INR)
WBC (total and differential)	Aspartate aminotransferase (AST)	Specific gravity	aPTT
Red Blood Cell Count	Lactate dehydrogenase (LDH)	Microscopic exam *(If abnormal)*	Total thriiodothyronine (T3)
Absolute Neutrophil Count	Carbon Dioxide ‡	results are noted	Free tyroxine (T4)
Absolute Lymphocyte Count	*(CO_2 or biocarbonate)*	Urine pregnancy test †	Thyroid stimulating hormone (TSH)
	Uric Acid		Blood for correlative studies
	Calcium		
	Chloride		
	Glucose		
	Phosphorus		
	Potassium		
	Sodium		
	Magnesium		
	Total Bilirubin		
	Direct Bilirubin *(If total bilirubin is elevated above the upper limit of normal)*		
	Total protein		
	Blood Urea Nitrogen		

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

‡ If considered standard of care in your region.

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 whenever possible. 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. Subjects who a) attain a CR or b) complete 24 months of treatment with pembrolizumab may discontinue treatment with the option of restarting treatment if they meet the criteria specified in Section 7.1.6.4. After discontinuing treatment following assessment of CR, these subjects should return to the site for a Safety Follow-up Visit (described in Section 7.1.6.1) and then proceed to the Follow-Up Period of the study (described in Section 7.1.6.2).

7.1.4.2 Blinding/Unblinding

This is an open-label trial.

7.1.5 Visit Requirements

Visit requirements are outlined in Section 6.0 - Schedule of Assessments. Specific procedure-related details are provided above in Section 7.1 - Trial Procedures.

7.1.6 Follow-up Requirements

7.1.6.1 Safety Follow-up Visit

The mandatory Safety Follow-up Visit should be conducted approximately 30 days after treatment discontinuation or before the initiation of a new anti-cancer treatment, whichever comes first. All AEs that occur prior to the Safety Follow-up Visit should be recorded. Subjects with an AE of Grade > 1 will be followed until the resolution of the AE to Grade 0-1 or until the beginning of a new anti-neoplastic therapy, whichever occurs first. SAEs that occur within 90 days of the end of treatment or before initiation of a new anti-cancer treatment should also be followed and recorded. Subjects who are eligible for retreatment with pembrolizumab (as described in Section 7.1.6.4) may have up to two Safety Follow-up Visits, one after the Treatment Period and one after the Retreatment Phase.

7.1.6.2 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 per institutional guidelines 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 7.1.6.4. 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 7.1.6.4 will move from the Follow-Up Phase to the Retreatment Period when they experience disease progression.

7.1.6.3 Survival Follow-up

Once a subject experiences confirmed disease progression or starts a new anti-cancer therapy, the subject moves into the survival follow-up phase and will be monitored every 6 months (± 30 days) to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

7.1.6.4 Retreatment Phase

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

Either

- Stopped initial treatment with pembrolizumab after attaining an investigator-determined confirmed CR according to RECIST 1.1 (Section 14.3), and
  - Was treated for at least 24 weeks with pembrolizumab before discontinuing therapy
  - Received at least two treatments with pembrolizumab beyond the date when the initial CR was declared

OR

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

AND

- Experienced an investigator-determined confirmed radiographic disease progression after stopping their initial treatment with pembrolizumab
- Did not receive any anti-cancer treatment since the last dose of pembrolizumab
- Has a performance status of 0 or 1 on the ECOG Performance Scale
- Demonstrates adequate organ function as detailed in Section 5.1.2
- Female subject of childbearing potential should have a negative serum or urine pregnancy test within 72 hours prior to receiving retreatment with study medication.
- Female subject of childbearing potential should be willing to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of study medication (reference Section 5.5.2). Subjects of child bearing potential are those who have not been surgically sterilized or have been free from menses for > 1 year.
- Male subject should agree to use an adequate method of contraception starting with the first dose of study therapy through 120 days after the last dose of study therapy.
- Does not have a history or current evidence of any condition, therapy, or laboratory abnormality that might interfere with the subject's participation for the full duration of the trial or is not in the best interest of the subject to participate, in the opinion of the treating investigator.

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

Visit requirements are outlined in Section 6.0 – Schedule of Assessments.

7.2 Assessing and Recording of Adverse Events

7.2.1 Definitions of Adverse Events

7.2.1.1 Adverse Event (AE)

An adverse event is defined as untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An adverse event can be ANY unfavorable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease temporarily associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product (attribution of 'unrelated', 'unlikely', 'possible', 'probable', or 'definite'). Adverse events will be graded according to the NCI Common Toxicity Criteria, Version 4.0.

7.2.1.2 Serious Adverse Event (SAE)

A serious adverse event is any untoward medical occurrence resulting in one or more of the following:

- Results in death or ANY death occurring within 90 days of last dose of study drug (even if it is not felt to be drug related)
- Is life-threatening (defined as an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalization or prolongation of existing hospitalization

NOTE: Hospitalizations that are not considered SAEs are:

  - Hospitalization planned prior to first administration of study drug
  - Hospitalization for elective treatment of a pre-existing condition unrelated to the study medication

- Results in persistent or significant disability/incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the patient or may require intervention (e.g., medical, surgical) to prevent one of the other serious outcomes listed in the definition above). Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions not resulting in hospitalization; or the development of drug dependency or drug abuse.
- Pregnancy

  - Pregnancy of a patient or of the female partner of a male patient during the study or within 120 days after the last dose of study drug should be reported via an SAE report. Should pregnancy occur in a female participant during the treatment period, study drug should be discontinued and Merck notified immediately. Should a pregnancy occur in a female companion of a male participant during the treatment period, the male participant can continue treatment and Merck notified immediately. Any such pregnancy is to be followed until final outcome. Evaluating Adverse Events
- In addition to the above criteria, AEs meeting either of the below criteria, although not serious per ICH definition, are reportable to Merck in the same time frame as SAEs to meet certain local requirements. Therefore, these events are considered serious by Merck for collection purposes.
  - Is a new cancer (that is not a condition of the study)
  - Is associated with an overdose of pembrolizumab

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.

7.2.1.3 Unanticipated Problem

Unanticipated Problem (UP)**:** any incident, experience, or outcome that meets all of the following criteria:

1) unexpected (in terms of nature, severity, or frequency) given (a) the research procedures are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being study;
2) related or possibly related to participation in the research; and
3) suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) related to the research than was previously known or recognized.

Only a small subset of adverse events occurring in human subjects participating in research will meet these three criteria for an unanticipated problem. Furthermore, there are other types of incidents, experiences, and outcomes that occur during the conduct of human subjects research that represent unanticipated problems but are not considered adverse events. For example, some unanticipated problems involve social or economic harm instead of the physical or psychological harm associated with adverse events. In other cases, unanticipated problems place subjects or others at increased risk of harm, but no harm occurs.

7.2.1.4 Unexpected Adverse Event

An adverse event not mentioned in the Investigator's Brochure or package insert or the specificity or severity of which is not consistent with the Investigator's brochure or package insert.

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

Table 6: Evaluating Adverse Events

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

V4.0 CTCAE Grading	**Grade 1**	**Mild; asymptomatic or mid symptoms; clinical or diagnostic observations only; intervention not indicated.**
	Grade 2	**Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.**
	Grade 3	**Severe or medically significant but not immediately life-threatening; hospitalization or prolongation or hospitalization indicated; disabling; limiting self-care ADL.**
	Grade 4	**Life threatening consequences; urgent intervention indicated.**
	Grade 5	**Death related to AE**
Seriousness	A serious adverse event is any adverse event occurring at any dose or during any use of pembrolizumab or vorinostat 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 pembrolizumab or vorinostat to be discontinued?	
Relationship to Pembrolizumab or Vorinostat	Did pembrolizumab or vorinostat cause the adverse event? The determination of the likelihood that pembrolizumab or vorinostat 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 pembrolizumab or vorinostat and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely pembrolizumab or vorinostat caused the adverse event (AE):	
	Exposure	Is there evidence that the subject was actually exposed to pembrolizumab or vorinostat 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 pembrolizumab or vorinostat? Is the time of onset of the AE compatible with a drug-induced effect?
	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 Pembrolizumab or Vorinostat (continued)	**The following components are to be used to assess the relationship between the test drug and the AE: (continued)**	
	Dechallenge	Was pembrolizumab or vorinostat 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 pembrolizumab or vorinostat; or (3) the trial is a single-dose drug trial); or (4) pembrolizumab or vorinostat are only used one time.)
	Rechallenge	Was the subject re-exposed to pembrolizumab or vorinostat 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) pembrolizumab or vorinostat 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 PEMBROLIZUMAB OR VORINOSTAT, OR IF REEXPOSURE TO PEMBROLIZUMAB OR VORINOSTAT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE SUBJECT, THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR AS PER DOSE MODIFICATION GUIDELINES IN THE PROTOCOL.
	Consistency with Trial Treatment Profile	Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the pembrolizumab or vorinostat 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 pembrolizumab or vorinostat relationship).**	
Yes, there is a reasonable possibility of pembrolizumab or vorinostat relationship.	There is evidence of exposure to pembrolizumab or vorinostat. The temporal sequence of the AE onset relative to the administration of pembrolizumab or vorinostat is reasonable. The AE is more likely explained by pembrolizumab or vorinostat than by another cause.	
No, there is not a reasonable possibility pembrolizumab or vorinostat relationship	Subject did not receive pembrolizumab or vorinostat OR temporal sequence of the AE onset relative to administration of the pembrolizumab or vorinostat is not reasonable OR there is another obvious cause of the AE. (Also entered for a subject with overdose without an associated AE.)	

7.2.2 Definition of an Overdose

For purposes of this trial, an overdose of pembrolizumab will be defined as any dose of 1,000 mg or greater (≥5 times the indicated dose). No specific information is available on the treatment of overdose of pembrolizumab. Appropriate supportive treatment should be provided if clinically indicated. An overdose of vorinostat will be defined as any dose of ≥5 times the current dose being given (i.e. if 100 mg is indicated, 500 mg would be considered treatment overdose, and if 200 mg is indicated, 1000 mg would be considered treatment overdose). In the event of overdose, the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

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

If a dose of investigational 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 as described in sections 7.2.5 and 10.5.

7.2.3 Pregnancy and Lactation

Although pregnancy and lactation are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them), including the pregnancy of a male subject's female partner that occurs during the trial or within 120 days of completing the trial, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier. All subjects and 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.

Such events must be reported as within 24 hours to the Sponsor and within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220)

7.2.4 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 and reported as described in sections 5.2.1.6 and 10.5. Events of Clinical Interest for this trial include:

1. An overdose of pembrolizumab, as defined in Section 7.2.2 - Definition of an Overdose, 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. Additional adverse events:

A separate guidance document has been provided entitled "Event of Clinical Interest Guidance Document" (previously entitled, "Event of Clinical Interest and Immune-Related Adverse Event Guidance Document"). This document can be found in Appendix 14.5 and provides guidance regarding identification, evaluation and management of ECIs and irAEs.

ECIs (both non-serious and serious adverse events) identified in this guidance document from the date of first dose through 90 days following cessation of treatment, or 30 days after the initiation of a new anticancer therapy, whichever is earlier, need to be reported as described in sections 5.2.1.6 and 10.5 regardless of attribution to study treatment, consistent with standard SAE reporting guidelines.

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

7.3 Participating Site Reporting Responsibilities

7.3.1 Reporting SAEs, ECIs and Pregnancy to the Coordinating Center (IU Simon Comprehensive Cancer Center)

Any serious adverse event, unanticipated problem, event of clinical interest or pregnancy occurring from the first dose of vorinostat to within 90 days from the last dose of study drug must be reported to the IU Simon Comprehensive Cancer Center within **24 hours** of notification or discovery of the incident, using the MedWatch Form 3500A (Mandatory Reporting). This form must be accompanied by a cover letter which: identifies the event, is signed by the local principal investigator or treating physician, includes the applicable study number and title, and contains the following:

- Site assessment of the event attribution to investigational treatment or study procedure
- Site assessment of event expectedness (expected vs. unexpected)

- Assessment of whether or not the research places subjects at a greater risk of harm than was previously known or recognized
- Assessment of the event's affect on the risk to benefit ratio
- Statement as to whether the informed consent statement should reflect changes in the potential risks involved
- Statement as to whether the event has been reported previously, and if so, whether the frequency is considered unusually high

Send to: IUSCC Clinical Trials Office
ATTN: Multicenter coordinator/ IUSCC-0551
Preferred E-mail: IUSCCSAE@iu.edu
Backup Fax: 317-944-3601

All SAEs must also be entered into OnCore for **monthly review** by the DSMC Coordinator. The Multicenter Network Administrator, or designee, will distribute all reports meeting expedited reporting criteria to all participating sites, the FDA and to Merck. Copies of all serious adverse event reports will be kept on file in the IU Simon Comprehensive Cancer Center Clinical Trials Office.

7.3.2 Follow-up of AE, SAE, and Other Reportable Safety Event Information

7.3.3 After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs, SAEs, and other reportable safety events including pregnancy and exposure during breastfeeding, events of clinical interest (ECIs), cancer, and overdose will be followed until resolution, stabilization, until the event is otherwise explained, or the participant is lost to follow-up.. In addition, the investigator will make every attempt to follow all nonserious AEs that occur in allocated or randomized participants for outcome. Reporting to the IRB

Each participating site will report SAEs, ECIs, pregnancies, and unanticipated problems to their IRB per local and institutional guidelines.

7.4 Coordinating Center Reporting Responsibilities

7.4.1 Reporting to the IRB

Unanticipated problems involving risks to subjects or others will be reported **promptly** to the IRB if they are:

- unexpected;
- related or possibly related to participation in the research; and
- suggests that the research places subjects or others at a greater risk of harm than was previously known or recognized.

If the unanticipated problem does not meet all three (3) criteria listed above, the event does not have to be promptly reported to the Indiana University IRB. However, it should be reported at the time of continuing review.

Prompt reporting of unanticipated problems to the IRB is defined as within 5 business days from becoming aware of the event.

7.4.2 Reporting to the FDA

Per CFR 312.32 (c), the investigator-sponsor of the IND must notify the Food and Drug Administration (FDA) and all participating investigators in a written IND safety report of any adverse experience. There are two types of reports to the FDA: 7-day and 15-day reports.

7-Day Reports:
The investigator-sponsor must notify the FDA and all participating investigators in a written IND safety report of any adverse experience:

- **fatal or life-threatening experience that is *both***
- **suspected to be associated with use of the drug *and***
- **unexpected (not in the investigator's brochure)**

The FDA will be notified as soon as possible but no later than **7 calendar days** after initial receipt of the information.

15-Day IND Reports:
Per CFR 312.32 (c), the investigator-sponsor of the IND must notify the Food and Drug Administration (FDA) and all participating investigators in a written IND safety report of any adverse experience:

- **suspected to be associated with use of the drug that is *both***
- **serious *and***
- **unexpected (not in the investigator's brochure)**

Each written notification shall be made as soon as possible, and no later than **15 calendar days** after the investigator-sponsor's initial receipt of the information.

Report Content
Each written notification may be submitted on FDA Form 3500A or in a narrative format and must bear prominent identification of its contents (i.e., "IND Safety Report"). For purposes of this protocol, the **MedWatch Report Form (FDA 3500A mandatory reporting), along with FDA Form 1571, and a cover letter** submitted to the appropriate FDA division, will serve as the written IND safety report. Follow-up information to a safety report should be submitted as soon as the relevant information is available.
Submit:

- MedWatch Report Form (FDA 3500A)
- FDA Form 1571
- Cover Letter

Notify the FDA via phone or fax using MedWatch 3500A (mandatory reporting form)

- Phone: 1-888-463-6332, option #1
- Fax: 1-800-FDA-0178

The IUSCC Protocol Development Coordinator should be contacted to assist with all FDA submissions and will be provided with a copy of all events that are reported to the FDA.

All IND submissions will be maintained in a master file in the IUSCC Clinical Trials Office.

7.4.3 Reporting to Merck

SAEs, ECIs and pregnancy reports and any other relevant safety information are to be forwarded to the Merck Global Safety facsimile number: +1-215-993-1220 within **2 working days** to Merck Global safety (Attn: Worldwide Product Safety; FAX 215 993-1220).

A copy of all 15 Day Reports and FDA Annual Progress Reports as required by the FDA will be submitted to Merck & Co., Inc. (Attn: Worldwide Product Safety; FAX 215 993-1220) at the time of submission to FDA. Investigators will cross reference this submission, according to local regulations, to the Merck Investigational Compound Number (IND) at the time of submission.

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

7.4.4 Reporting to Participating Sites

For IND safety reports originating from this study, IUSCC will distribute reports which are serious, unexpected and suspected to be associated with the study intervention (possibly, probably or definitely related) to all participating sites in the form of an Expedited Safety Report (external safety/IND report) within 15 calendar days from determination that the suspected adverse reaction qualifies for reporting. Copies of these Expedited Safety Reports will be kept on file in the IU Simon Comprehensive Cancer Center Clinical Trials Office.

When the sponsor(s) sends IND safety reports from external studies that involve the study drug(s), Multicenter Network Associate Administrator, or designee, will forward the reports to the sponsor-investigator. The sponsor-investigator, or designee, will review these reports and determine if revisions are needed to the protocol or consent. IUSCC will forward these reports to participating sites every 2 weeks.

If an adverse event or SAE requires modification of the informed consent, protocol or other study documents, participating sites will be informed by way of an amendment and during weekly teleconferences, or sooner, as deemed necessary by the Principal Investigator.

7.4.5 Reporting to the IUSCC Data Safety Monitoring Committee (DSMC)

Regardless of study sponsorship, the study team must enter all initial and follow-up SAEs, expedited, and noncompliance reports into OnCore® for review by the DSMC chair and/or

coordinator. Expedited reports may include IRB Prompt Report Forms, MedWatch, and additional SAE forms as required by the sponsor. When follow-up information is received, a follow-up report should also be created in OnCore®. This DSMC reporting requirement is in addition to any other regulatory bodies to be notified (i.e. IRB, FDA, pharmaceutical company, etc.). The DSMC chair and/or coordinator will review all SAE, expedited, and noncompliance reports monthly.

8.0 STATISTICAL METHODS

8.1 General Considerations

Statistical analysis of this study will be the responsibility of the Department of Biostatistics at Indiana University School of Medicine. Parameter estimates and relevant summary statistics will be reported for both efficacy and safety outcomes. Continuous variables will be summarized by means, medians, minima, maxima and standard deviations. Categorical variables will be summarized by frequencies and percentages. Missing data will not be imputed. Additional exploratory analysis will be conducted when appropriate. Changes from the analysis plan will not require an amendment to the protocol unless it changes a significant feature in the protocol. The statistical analysis methods are outline below.

8.2 Study Design

This is an open-label phase I/Ib clinical trial. No randomization or blinding is involved.

8.3 Analysis Populations

8.3.1 Efficacy Population

The efficacy population comprises all patients who meet the eligibility criteria, are registered onto the study, get at least one dose of study drug, and have at least one follow-up evaluation. This set will be used for efficacy analysis.

8.3.2 Safety Population

The safety population comprises all patients who have received at least one dose of the study medication. This set will be used for safety analysis.

8.4 Sample Size, Accrual and Study Duration

A minimum of 51 and maximum of 57 subjects (3-6 per 2 dose levels in the escalation phase + 45 in three expansion cohorts) will be enrolled in this study. The primary sample size is dictated by the 3+3 design described earlier. Subjects not DLT evaluable in the finding phase will be replaced. Three expansion cohorts of up to n = 15 subjects each will be used to measure efficacy endpoints and is critical for the planning of the next phase of investigation. Having at least 12 patients per expansion cohort is adequate for the purposes of estimating effect sizes for larger trials for outcomes that are normally distributed or can be transformed to normality.[10] Increasing to 15 per group will help account for the possibility that a few subjects may not be evaluable for efficacy. Subjects not evaluable for efficacy in the expansion phase will be replaced. A subject is not evaluable for efficacy if they do not have at least one follow-up assessment of disease status after completing 1 cycle of combination

therapy. This could be either a scan or an assessment of symptomatic deterioration. Accrual is expected to take up to 12 months.

8.5 Patient Characteristics

Baseline patient characteristics will be tabulated, such as demographics (age, race, gender), and disease characteristics.

8.6 Significant Protocol Violations

Significant protocol violations such as with respect to eligibility criteria and treatment plan will be tabulated.

8.7 Concomitant Medications

Drugs that might affect the study medication will be tabulated.

8.8 Exposure and Compliance

Exposure to the study medication will be summarized by frequencies and rates of the doses given. Reasons of not completing all doses will be tabulated.

8.9 Efficacy Analysis

Responses will be tabulated and objective response (CR+PR) via RECIST 1.1 will be summarized with the point estimate and corresponding exact 95% confidence interval. For patients with prostate cancer PSA response (≥50% decline from baseline), PSA progression (≥50% increase from baseline/nadir) and bone lesions progression on ^{68}Ga-PSMA-11 PET or bone scans (≥2 lesions from baseline with confirmatory scans 6 weeks later showing ≥2 additional lesions) will be reported. Progression free and overall survival will be estimated using standard Kaplan-Meier curves. The median time-to-event for each endpoint will be estimated along with the corresponding 95% confidence interval. Similar descriptive analyses will be performed using irRC criteria. Endpoints such as quantitative characteristics of humoral immune response will be characterized by their mean and corresponding 95% confidence interval. No statistical comparisons are planned. Analyses will be done separately by each expansion cohort. Patients enrolled in the Dose Finding Phase will be excluded when estimating efficacy for the design of a future trial.

8.10 Safety Analysis

Toxicities according to CTCAE 4.0 (see Section 14.2) will be summarized by frequencies and rates calculated as the proportion of patients in the safety population experiencing SAEs, discontinuations due to AEs, and AEs. Two sets of tables will be generated: one for the overall toxicities and one for toxicities related to the study medication (possibly related, probably related and definitely related). Toxicities will be grouped by system using MedRA preferred terminology. Grade 1 to 4 will be reported individually and also as grade 3/4. Deaths will be reported individually. AEs will be reported by dose finding cohort. In the Dose Finding Phase, DLT's will be evaluated in the first 21 days of therapy (see Section

5.2.1.3). The AEs during the expansion phase will also be reported separately by expansion cohort.

Toxicity monitoring in the expansion phase will be continuous with each expansion arm monitored separately. We will consider the treatment to be excessively toxic if the probability of dose limiting toxicities in the first 21 days of therapy is 33% or greater. The following table is based on exact binomial probabilities dropping below 0.10, which we will define as an unlikely possibility:

Stop if number of DLTs is:	3	4	5	6	7	8
in N patients	3	4-6	7-8	9-10	11-13	14-15

8.11 Interim Analysis

No interim efficacy analysis will be performed

9.0 DATA AND SAFETY MONITORING

This study will be conducted in accordance with the IU Simon Comprehensive Cancer Center Institutional DSMP for High Risk Trials.

Investigators will conduct continuous review of data and subject safety. Weekly review meetings for high risk trials are required and will include the principal investigator, clinical research specialist and/or research nurse (other members per principal investigator's discretion). Weekly meeting summaries should include review of data and subject safety by including for each dose level: the number of subjects, significant toxicities as described in the protocol, dose adjustments and responses observed. Study teams should maintain meeting minutes and attendance for submission to the DSMC upon request.

9.1 Data Safety Monitoring Committee

The IUSCC Data and Safety Monitoring Committee (DSMC) is responsible for oversight of subject safety, regulatory compliance, and data integrity for this trial. The DSMC will review this study semi-annually to review overall trial progress, toxicity, compliance, data integrity, and accrual per the Institutional DSMP.

Furthermore, the DSMC conducts an administrative review of serious adverse events (SAEs), deviations, reportable events, and any other outstanding business. Major issues may require further DSMC review or action.

For any increase in frequency of grade 3 or above adverse events (above the rate reported in the Investigator Brochure or package insert), the principal investigator will notify the DSMC Chair immediately. The notification will include the incidence of study adverse events, grades, and attributions, as well as investigator statements regarding comparison with risks per the IB/ package insert.

At any time during the conduct of the trial, if it is the opinion of the investigators that the risks (or benefits) to the subject warrant early closure of the study, the DSMC Chair and Compliance

Officer must be notified within 1 business day via email, and the IRB must be notified within 5 business days. Alternatively, the DSMC may initiate suspension or early closure of the study based on its review.

9.2 DSMC DLT Review

The principal investigator and study statistician will officially review all toxicity for each cohort of subjects prior to making dose escalation/expansion/de-escalation decisions. Once a decision has been reached by the investigator, the official decision and toxicity data will be submitted to the DSMC via email (IUSCC-DLT-Review-L@list.iupui.edu). Treating additional subjects may not proceed until official DSMC correspondence confirms approval of dosing decisions for the next stage.

9.3 IND Annual Reports

For trials with an IND held locally by the IU principal investigator or university, the IND Annual Report will be prepared and submitted to the Compliance Team. This report will be reviewed and approved by the DSMC prior to FDA submission.

9.4 Study Auditing and Monitoring

All trials conducted at the IUSCC are subject to auditing and/or monitoring per the Institutional DSMP. Reports will be reviewed by the full DSMC at the time of study review.

9.5 Data Management/ Oncore Reporting Requirements

The DSMC reviews data and study progress directly from Oncore; therefore, timely data entry and status updates are vital. Study data must be entered within Oncore promptly, no later than one week from study visit occurrence. Subject status in Oncore will be updated in real time, as this may affect overall trial enrollment status. Global SAEs and deviations will be reviewed on a monthly basis by the DSMC Chair directly from Oncore.

9.6 Study Accrual Oversight

Accrual data will be entered into the IU Simon Comprehensive Cancer Center OnCore system. The Protocol Progress Committee (PPC) reviews study accrual twice per year, while the PPC coordinator reviews accrual quarterly.

9.7 Oncore Safety Reporting

In addition to protocol- and regulatory-required safety reporting, all serious adverse events (SAEs) will be captured in the Oncore system within 1 business day of notification. Initial SAE reporting will include as much detail as available, with follow-up to provide complete information. Attributions will be assessed to study drugs, procedures, study disease, and other alternate etiology.

9.8 Protocol Deviation Reporting

Protocol deviations will be entered into OnCore within 5 days of discovery and reviewed by the DSMC Chair on a monthly basis. Findings will be reported to the full DSMC at the time of study review. For serious or repetitive protocol deviations, additional action may be required by the DSMC.

9.9 Data Acquisition

Case Report Forms and Data Submission: This study will utilize electronic Case Report Form completion in the OnCore® database. A calendar of events and required forms are available in OnCore® at https://cancer.iu.edu/oncore. The OnCore® database is a comprehensive database used by the IUSCC CTO and supported by the Indiana University Cancer Center.

Access to data through OnCore® is restricted by user accounts and assigned roles. Once logged into the OnCore® system with a user ID and password, OnCore® defines roles for each user which limits access to appropriate data.

All source documents are to remain in the patient's clinic file. All documents should be kept according to applicable federal guidelines. Clinical trial data in OnCore® are periodically monitored by the IU Simon Comprehensive Cancer Center per the DSMC Charter.

10.0 MULTICENTER GUIDELINES

10.1 Study Documents

Each participating site must submit regulatory documents (informed consents, 1572s, Financial Disclosures, IRB approval documents, Continuing Reviews, Amendments, patient brochures or recruitment material etc.) to the Coordinating Center. The Coordinating Center will provide each site with a comprehensive list of the required documents prior to study start-up, throughout the duration of the study and upon study close-out. It is the responsibility of the participating site to maintain copies of all documentation sent to the Coordinating Center.

10.2 Study Initiation

Before activating the clinical trial at each participating site, the IUSCC CTO Multicenter Network Administrator , or designee, will ensure that:

- Full **Institutional Review Board (IRB) approval** has been obtained.
- Research staff at the participating site has been trained in data entry into *OnCore*®
- A **start-up meeting** with each institution has taken place via telephone conference. The start-up meeting will cover protocol details (including eligibility

criteria, treatment plan, etc.), responsibilities of the participating investigators, and reporting procedures.
- A financial **conflict of interest statement** from each investigator has been obtained.

10.3 Patient Enrollment

After eligibility is confirmed by the participating site staff, a completed eligibility checklist, supporting source documentation, and signed consent will be sent to IUSCC for verification. The Multicenter Network Administrator, or designee, will confirm eligibilityand return the enrollment information to the site. The site staff will then register the patient in OnCore®. Additional details of this process can be found in the Study Procedure Manual.

10.4 Data Monitoring

All multicenter investigator initiated trials conducted at the IUSCC are subject to data monitoring by the Multicenter Network Administrator, or designee. External sites will be notified of upcoming monitoring visits and will be expected to provide the Multicenter Network Administrator, or designee, with source documents for remote monitoring of patients. Queries will be issued in OnCore® and a detailed monitoring report will be provided to the participating site. The IUSCC will also forward any monitoring and/or auditing reports to the DSMC.

When a patient enrolled on this trial, or the trial itself, is selected for local monitoring or auditing, the participating site will forward the results to the Multicenter Network Administrator, or designee. In addition, if a participating site patient is selected for local auditing by the IUSCC DSMC, the site will be responsible for sending IUSCC de-identified source documents.

10.5 Record Retention

All documentation of adverse events, records of study drug receipt, dispensation, destruction, and all IRB correspondence will be stored in accordance with all applicable federal guidelines.

Following closure of the study, each participating site will maintain a copy of all site study records in a safe and secure location. The Coordinating Center will inform the investigator at each site at such time that the records may be destroyed.

11.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

11.1 Investigational Product

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of

investigational product in accordance with the protocol and any applicable laws and regulations.

Clinical Supplies will be provided by Merck as summarized in Table 7.

Table 7: Product Descriptions

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

11.2 Packaging and Labeling Information

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

11.3 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.

11.4 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.

11.5 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.

12.0 ADMINISTRATIVE AND REGULATORY DETAILS

12.1 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.

13.0 REFERENCES

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14.0 APPENDICES

14.1 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.	

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

Due to the size of the latest version of the Common Toxicity Criteria, copies of this appendix are not included with this protocol document. An electronic copy is available on the CTEP web site, http://ctep.cancer.gov/reporting/ctc.html**.**

14.3 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. The same imaging technique regarding modality, ideally the same scanner, and the use of contrast should be used in a participant throughout the study to optimize the reproducibility of the assessment of existing and new tumor burden and improve the accuracy of the assessment of response or progression based on imaging.

* 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.

14.3.1 Tumor Imaging and Assessment of Disease

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

Expedited confirmation of measurable disease based on RECIST 1.1 at Screening should be used to determine participant eligibility. Confirmation that the participant's imaging shows at least 1 lesion that is appropriate for selection as a target lesion per RECIST 1.1 is highly recommended prior to participation starting treatment.

Participant eligibility will be determined using local assessment (Investigator assessment) based on RECIST 1.1. In addition, images (including via other modalities) that are obtained at an unscheduled time point to determine disease progression, as well as imaging obtained for other reasons, but which demonstrate radiologic progression, should also be used to determine progression.

When the Investigator identifies radiographic progression per RECIST 1.1, efforts should be made to verify radiologic PD. Treatment should continue until PD has been verified.

14.3.2 Initial Tumor Imaging

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

The screening images must be submitted to the central imaging vendor for confirmation of measurable disease per RECIST 1.1 for eligibility prior to start of treatment.

Tumor imaging performed as part of routine clinical management is acceptable for use as screening tumor imaging if they are of diagnostic quality and performed within 28 days prior to the date of cycle 1 and can be assessed by the central imaging vendor.

14.3.3 Tumor Imaging During the Study

The first on-study imaging assessment should be performed at 4 weeks (28 days -7 days) from the date of screening. Subsequent tumor imaging should be performed every 9 weeks (63 days ±3 days) or more frequently if clinically indicated. After 18 weeks (126 days ±3 days), participants who remain on treatment will have imaging performed every 9 weeks (63 days ±3 days). Imaging timing should follow calendar days and should not be adjusted for

delays in cycle starts. Imaging should continue to be performed until disease progression is identified by the Investigator.

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

14.3.4 End of Treatment and Follow-up Tumor Imaging

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

For participants who discontinue study treatment without documented disease progression, every effort should be made to continue monitoring their disease status by tumor imaging using the same imaging schedule used while on treatment (every 9 weeks in Year 1 or every 6 months after Year 1) to monitor disease status until the start of a new anticancer treatment, disease progression, pregnancy, death, withdrawal of consent, or the end of the study, whichever occurs first.

14.3.5 Second Course (Retreatment) Tumor Imaging

Tumor imaging must be performed within 10 days prior to restarting treatment with pembrolizumab. Local reading (Investigator assessment with site radiology reading) will be used to determine eligibility.

The first on-study imaging assessment should be performed at 9 weeks (63 days ±3 days) after the restart of treatment. Subsequent tumor imaging should be performed every 9 weeks (63 days ±3 days) or more frequently, if clinically indicated.

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

Imaging should continue to be performed until disease progression, the start of a new anticancer treatment, withdrawal of consent, death, or notification by the Sponsor, whichever

occurs first. Disease progression may be confirmed 4 to 8 weeks after the first tumor imaging indicating PD, in clinically stable participants.

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

For participants who discontinue study treatment without documented disease progression, every effort should be made to continue monitoring their disease status by radiologic imaging every 6 months (180 days ±14 days) until either the start of a new anticancer treatment, disease progression, pregnancy, death, or the end of the study, whichever occurs first.

14.4 Drug Diary

Patient Medication Diary

Patient ID _____ **Date** _____

Patient Initials _____ **Vorinostat Dose** _____

Day	Date			Time		Please note any unusual symptoms
	Month	Day	Year	Time	AM/PM	
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
13						
14						

Date of pill bottle return _____ **Nurse Signature** _____

14.5 Events of Clinical Interest Guidance Document

Attached as PDF entitled, "Pembrolizumab ECI_Guidance Document_Version 5_FINAL_18-Dec-2014"

14.6 Woman of Childbearing Potential (WOCBP) definition

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

Women in the following categories are not considered WOCBP:

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

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

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

14.7 Immune-Related Response Criteria

INTRODUCTION

Increasing clinical experience indicates that traditional response criteria (e.g., Response Evaluation Criteria in Solid Tumors, Version 1.1 [RECIST v1.1] and World Health Organization [WHO]) may not be sufficient to characterize fully activity in the new era of target therapies and/or biologics. In studies with cytokines, cancer vaccines, and monoclonal antibodies, complete response, partial response, or stable disease has been shown to occur after an increase in tumor burden as characterized by progressive disease by traditional response criteria. Therefore, conventional response criteria may not adequately assess the activity of immunotherapeutic agents because progressive disease (by initial radiographic evaluation) does not necessarily reflect therapeutic failure. Long-term effect on the target disease must also be captured. The immune-related response criteria[1] (irRC) are criteria that attempt to do that by enhancing characterization of new response patterns that have been observed with immunotherapeutic agents (i.e., ipilimumab). (Note: The irRC only index and measurable new lesions are taken into account.)

GLOSSARY

Term	Definition
SPD	sum of the products of the two largest perpendicular diameters
Tumor burden	$SPD_{\text{index lesions}} + SPD_{\text{new, measurable lesions}}$
Nadir	minimally recorded tumor burden
irCR	immune-related complete response
irPD	immune-related progressive disease
irPR	immune-related partial response
irSD	immune-related stable disease
irBOR	immune-related best overall response

BASELINE ASSESSMENT USING irRC

Step 1. Identify the index lesions (five lesions per organ, up to ten visceral lesions and five cutaneous lesions).

Step 2. Calculate the SPD of all of these index lesions:

$$\text{SPD} = \sum_{i} \text{(Largest diameter of lesion i)} \times \text{(Second largest diameter of lesion i).}$$

[1] Wolchok JD, Hoos A, O'Day S, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. Clin Can Res 2009;15:7412–20.

POST-BASELINE ASSESSMENTS USING irRC

Step 1. Calculate the SPD of the index lesions.

Step 2. Identify new, measurable lesions ($\geq 5 \times 5$ mm; up to five new lesions per organ: five new cutaneous lesions and ten visceral lesions).

Step 3. Calculate the SPD of the new, measurable lesions.

Step 4. Calculate the tumor burden:

$$\text{Tumor burden} = \text{SPD}_{\text{index lesions}} + \text{SPD}_{\text{new, measurable lesions}}$$

Step 5. Calculate the change in tumor burden relative to baseline and the change in tumor burden relative to nadir.

Step 6. Derive the overall response using the table below.

Overall Response	Criterion
irCR	Complete disappearance of all lesions (whether measurable or not, and no new lesions) confirmed by a repeat, consecutive assessment ≥4 weeks from the date first documented
irPR	Decrease in tumor burden ≥50% relative to baseline confirmed by a consecutive assessment ≥4 weeks from the date first documented
irSD	Criteria for irCR, irPR, and irPD are not met; does not require confirmation
irPD	Increase in tumor burden ≥25% relative to nadir confirmed by a consecutive assessment ≥4 weeks from the date first documented

irCR = immune-related complete response; irPD = immune-related progressive disease;
irPR = immune-related partial response; irSD = immune-related stable disease.

DETERMINATION OF irBOR

Once a patient has completed all tumor assessments, his/her irBOR may be determined:

Condition	irBOR
At least one irCR	irCR
At least one irPR and no irCR	irPR
At least one irSD and no irCR and no irPR	irSD
At least one irPD and no irCR, no irPR, and no irSD	irPD

irBOR = immune-related best overall response; irCR = immune-related complete response;
irPD = immune-related progressive disease; irPR = immune-related partial response;
irSD = immune-related stable disease.