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Epigenetic priming for Immune therapy in ER-positive breast cancer in biomarker select population

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Protocol Signature Page

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1. I agree to follow this protocol version as approved by the UCSF Protocol Review Committee (PRC), Institutional Review Board (IRB), and Data and Safety Monitoring Committee (DSMC).
2. I will conduct the study in accordance with Good Clinical Practices (ICH-GCP) and the applicable IRB, ethical, federal, state, and local regulatory requirements.
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Abstract

Title	Epigenetic priming for Immune therapy in ER-positive breast cancer in biomarker select population (Pembrolizumab, Vorinostat, Tamoxifen)
Study Description	We propose a randomized two-arm trial, enrolling 65 patients with hormone therapy-resistant breast cancer (HTR) to test the role of epigenetic priming in a biomarker enriched patient population in HTR breast cancer.
Phase of Study	Phase II
Investigational Products	Pembrolizumab, Vorinostat, Tamoxifen
Study population	Pre- and postmenopausal women or men with stage IV ER+ breast cancer with histological or cytological confirmation, 18 years or older
Primary Objective	To define the role of epigenetic immune priming in a biomarker enriched ER+ breast cancer population on the basis of overall response rate (ORR: CR+PR+SD at 24 weeks).
Secondary Objectives	a) To assess duration of response (DOR) 24-week landmark progression-free survival (PFS:24) b) Median PFS and overall survival (OS) c) Tumor responses will also be calculated by Immune Related Response-Criteria (irRC).

Exploratory Objectives	a) Evaluation of biomarker target threshold on response rate (retrospective cut off of 20% vs. 10%) b) To assess the ratio of effector T cells: regulatory T cells in blood and tumor biopsies pre- and post-therapy. c) To evaluate inflammatory T cell signature changes in blood and tumor biopsies pre- and post-therapy. d) To evaluate changes in number of myeloid-derived suppressor cells (MDSCs) in peripheral blood and tumor biopsies pre- and post-therapy. e) To evaluate changes in histone acetylation in peripheral blood cells and tumor biopsies pre- and post-therapy f) (Initial comparison to vorinostat-induced PD-1 in lymphocytes, PD-L1 modulation g) Nanostring and 10x sequencing and single cell immune phenotyping (on stored tissue for successful arms only) h) Impact of HDAC inhibition of response to pembrolizumab vs. pembrolizumab in biomarker enriched population
Sample Size	Arm A (pembro + vorinostat + TAM): A total of 35 patients will be accrued. Arm B (pembro + TAM): A total of 30 patients will be accrued. Total of 65 patients will be accrued.
Duration of Study Treatment	Patients may continue treatment until development of toxicity or until the patient no longer experiences clinical benefit.
Duration of Follow up	Patients will be followed for 30 days after end of study participation or removal from study, and serious adverse events will be collected for 30 days after the end of treatment should the patient be taken off therapy.
Unique Aspects of this Study	This is one of the first studies to look at the response of hormone therapy-resistant breast cancer to epigenetic immune priming and the combination of an HDAC inhibitor (vorinostat), an anti-estrogen (tamoxifen) and a PD-1 inhibitor (pembrolizumab) in pre or postmenopausal patients with ER+ advanced breast cancer with progression on multiple prior therapies in a biomarker-enriched population. The goal of this study is to demonstrate that HDAC induced epigenetic priming in a biomarker enriched study will increase the efficacy of pembrolizumab with patient selection based on exhausted CD8+ cells in blood or tumor in a small subset of (ER)+ breast cancer patients.

List of Abbreviations

AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BUN	blood urea nitrogen
CBC	complete blood cell (count)
CNS	central nervous system
CR	complete response
CRF	case report form
CT	computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTMS	Clinical Trial Management System
DFS	disease-free survival
DLT	dose-limiting toxicity
DSMC	Data and Safety Monitoring Committee
DSMP	Data and Safety Monitoring Plan
ECG/EKG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
FDA	Food and Drug Administration
FDG	Fluorodeoxyglucose
FLC	free light chain
GCP	Good Clinical Practice
GFR	glomerular filtration rate
HBeAg	hepatitis B “e” antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HDFCCC	Helen Diller Family Comprehensive Cancer Center
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Conference on Harmonization
IDS	Investigational Drug Services (UCSF)
IND	investigational new drug application
IP	investigational product

List of Abbreviations

IRB	Institutional Review Board
IV	intravenous
LDH	lactate dehydrogenase
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCI	National Cancer Institute
ORR	overall response rate
PD	disease progression
PK	pharmacokinetics
PO	*Per os* (by mouth, orally)
PR	partial response
PRC	Protocol Review Committee (UCSF)
SD	stable disease
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase

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1 Introduction

1.1 Background on Indication

1.1.1 Introduction to breast cancer

Breast cancer is one of the most common cancers in the western hemisphere and the second most common cause of cancer death in women[1]. Endocrine therapy (including ovarian ablation, estrogen administration, and more recently, antiestrogen administration) has been a major component of antitumor therapy in breast cancer for more than a century[2]. Hormone-sensitive metastatic breast cancer remains a therapeutic challenge despite the many recent advances in therapy as these tumors are frequently less sensitive to chemotherapy[3]. Barring a few exceptions, cure is not achieved in this disease. While hormonal interventions have clearly been shown to decrease tumor burden and to prolong life, the majority of patients eventually succumb to their disease due to disease recurrence.

1.1.2 Hormone-sensitive breast cancer

More than two-thirds of all advanced breast cancers are dependent on estrogen. Estrogen withdrawal by physical removal of the ovaries or inhibition of their function has been one of the earliest successful interventions against breast cancer; however, this intervention was limited to premenopausal women. The introduction of the SERMS (selective estrogen receptor modulators) has dramatically improved the survival of women with breast cancer, both pre- and post-menopausal. The most prominent SERM is tamoxifen, which until recently has been the gold standard for first-line therapy in women with advanced hormone-sensitive breast cancer. The production of estrogen in postmenopausal women requires an enzyme called aromatase, which can be successfully blocked chemically. The introduction of several aromatase inhibitors (AIs) has added greatly to the arsenal against breast cancer, and they have replaced tamoxifen as first-line therapy in the postmenopausal setting. The most commonly used aromatase inhibitors include letrozole, anastrozole, and exemestane.

However, the AIs are reserved for women who have naturally entered menopause or have their ovarian function suppressed. For premenopausal women or women who are unable to tolerate AIs, tamoxifen remains the gold standard.

The response rate to first-line hormonal therapy, determined from four pivotal randomized Phase III trials, ranges from 20-33%[4-7]. The response rate to second-line hormonal therapy is considerably less (10-20%)[4], suggesting a clear need for more effective therapy[8-10].

1.1.3 Therapy resistance in breast cancer

Breast cancer has now been subclassified into several major subgroups: hormone therapy sensitive, hormone therapy-resistant (HTR), HER2 positive (HER2+), and triple negative (TN). The treatment approaches to these clinical subtypes vastly differ. Hormone resistance has been attributed to a number of different mechanisms, namely loss of ER expression, alterations in apoptosis and cell signaling pathways, changes in ER coregulators, and the development of escape pathways[11]. Therefore, these women receive minimal benefit from endocrine therapy. The development of hormone therapy resistance is one of the most frequent causes of cancer death in women worldwide.

1.2 Background on the Investigational Products and Associated Known Toxicities

1.2.1 Pembrolizumab/MK-3475

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

Pembrolizumab (previously known as SCH 900475) 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.

1.2.1.1 Pharmaceutical and Therapeutic Background of PD-1

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades[12]. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies[13-17]. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells / FoxP3+ regulatory T-cells correlates with improved prognosis and long-term survival in many solid tumors.

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1 expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an Ig superfamily member related to CD28 and CTLA-4 which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD L2)[1,2]. The structure of murine PD-1 has been resolved[3]. PD-1 and family members are type I transmembrane glycoproteins containing an Ig Variable-type (V-type) domain responsible for ligand binding and a cytoplasmic tail which is responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM).

Following T-cell stimulation, PD 1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3ζ, PKCθ, and ZAP70 which are involved in the CD3 T-cell signaling cascade[1,4-6]. The mechanism by which PD-1 downmodulates T-cell responses is similar to, but distinct from that of CTLA-4 as both molecules regulate an overlapping set of signaling proteins[7,8]. PD-1 was shown to be expressed on activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B-cells, T regs and Natural Killer cells[9,10]. Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells[11]. The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types, including non-hematopoietic tissues as well as in various tumors[7,18-20]. Both ligands are type I transmembrane receptors containing both IgV- and IgC-like domains in the extracellular region and contain short cytoplasmic regions with no known signaling motifs. Binding of either PD-1 ligand to PD-1 inhibits T-cell activation triggered through the T-cell receptor. PD-L1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments. PD-L2 is thought to control immune T-cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T-cell function in peripheral tissues[7]. Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor. PD-1 has been suggested to regulate tumor-specific T-cell expansion in subjects with melanoma (MEL)[21]. This suggests that the PD-1/PD-L1 pathway plays a critical role in

tumor immune evasion and should be considered as an attractive target for therapeutic intervention.

1.2.1.2 Pre-clinical and Clinical Trials

Therapeutic studies in mouse models have shown that administration of antibodies blocking PD-1/PD-L1 interaction enhances infiltration of tumor-specific CD8+ T-cells and leads ultimately to tumor rejection, either as a monotherapy or in combination with other treatment modalities. Anti-mouse PD-1 or anti-mouse PD-L1 antibodies have demonstrated anti-tumor responses as a mono-therapy in models of squamous cell carcinoma, pancreatic carcinoma, MEL, and colorectal carcinoma. Blockade of the PD-1 pathway effectively promoted CD8+ T-cell infiltration into the tumor and the presence of IFN-ɣ, granzyme B, and perforin, indicating that the mechanism of action involved local infiltration and activation of effector T-cell function in vivo[22-27]. Experiments have confirmed the in vivo efficacy of PD-1 blockade as a monotherapy as well as in combination with chemotherapy in syngeneic mouse tumor models (see the Investigator's Brochure [IB]).

For trial details, please refer to the Investigator's Brochure. Pembrolizumab has been approved in several indications, see FDA label and IB v 16.

1.2.2 Suberoylanilide hydroxamic acid (Vorinostat, SAHA)

Vorinostat (Suberoylanilide hydroxamic acid, SAHA; NSC 701852) is a small molecule inhibitor of histone deacetylase (HDAC) that binds directly in the enzyme's active site in the presence of a zinc ion[28]. Because aberrant HDAC activity has been implicated in a variety of cancers, development of HDAC inhibitors is a rational approach to the design of targeted anticancer therapeutics. Several HDAC inhibitors from multiple chemical classes have been developed and are currently in clinical trials. Trichostatin A and butyric acid were among the first HDAC inhibitors to be administered to patients, but these were found to be clinically unsuitable due to potency and formulation issues[29,30]. Depsipeptide was originally selected for clinical study based on its antiproliferative effects; subsequently, it was discovered to antagonize HDACs and was the first HDAC inhibitor to demonstrate clinical efficacy[31]. Of the three classes of HDACs, vorinostat targets most human Class 1 (related to the yeast transcriptional regulator Rpd3) and Class 2 (similar to the yeast Hda1) enzymes[32,33]. The third class of HDACs (homologs of yeast sir2) requires NAD+ for activity and is not inhibited by vorinostat. Among those currently in clinical trials, vorinostat is the most potent HDAC inhibitor that can be administered orally with excellent bioavailability. Vorinostat was the first HDAC approved for CTCL in 2006.

Vorinostat was identified originally by its ability to induce differentiation of murine erythroleukemia cells at micromolar concentrations[34]. Subsequently, it was found to induce differentiation or arrest growth of a wide variety of human carcinoma cells. To date, vorinostat activity has been reported in transformed hematopoietic cells, including multiple myeloma (MM), acute promyelocytic leukemia (APL), acute lymphocytic leukemia, chronic myelogenous leukemia, Waldenstrom's macroglobulinemia, and cutaneous T-cell lymphoma (CTCL)[35-39]. Activity has also been reported in cell lines representing other tumor types, including bladder transitional cell carcinoma, breast cancer, prostate cancer, head and neck squamous carcinoma, and colon carcinoma[40-45].

The antitumor activity of vorinostat was demonstrated in several in vivo models of cancer, including a xenograft model of human CWR22 prostate cancer cells[41], a mouse model of APL containing the promyelocytic leukemia zinc-finger-retinoic acid receptor α fusion gene (PLZF-RARα)[46], and an N-methylnitrosourea-induced mammary tumor model in rodents[47]. Vorinostat has also shown activity when administered daily by intraperitoneal (IP) injections in the CWR22

and PLZF-RARα models and by oral (PO) administration in the carcinogen-induced mammary tumor model.

1.2.3 Tamoxifen

Tamoxifen is the most commonly used selective estrogen receptor modulator, SERM. It is currently being used for the prevention of breast cancer, for ductal carcinoma in situ, in women with early stage breast cancer and for those with metastatic cancer. It is generally well tolerated, and due to its extensive use, its toxicities and long-term sequelae are well characterized. Women being treated with tamoxifen may experience flushing (similar to the flushing women experience during menopause), vaginal dryness, and vaginal discharge. The most serious side effect is the slightly increased risk of thromboembolic events. In a trial involving 900 women treated with either tamoxifen or letrozole, 9 out of 455 patients experienced a thromboembolic event (2%), compared to 3 patients out of 455 in the group treated with letrozole (<1%). Other side effects included hot flashes (25%), headaches (5%), fatigue (5%), and nausea (8%)[7]. The observation of endometrial cancer (<0.5%) has been predominantly observed when used in the preventive or adjuvant setting[48]. Hence, the cumulative administration of tamoxifen is rarely hampered by toxicity, but rather by the emergence of resistance suggested by clinical progression while on the drug.

1.2.4 Histone Deacetylases (HDAC) and their inhibitors

A promising new class of drugs showing activity in cancer is the histone deacetylase inhibitors (HDACi)[32,49]. While these agents may have single-agent activity in cancer, they may also sensitize certain cancers to other types of therapeutic agents or overcome resistance. Histone deacetylases (HDAC) function to modulate gene expression by the removal of acetyl groups from histones[50,51]. The addition of acetyl groups to lysine residues on the N-terminal tail of histones by histone acetyltransferases (HAT) results in the weakening of the bond between histones and DNA[51].

In contrast, removal of acetyl groups by HDACs results in the condensation of the nucleosomes and has been correlated with gene silencing[51]. HDACs can be divided into at least three different classes, I-III. Each class contains several members of structurally and functionally variable HDACs[52,53]. Alterations in the regulatory function of HATs and HDACs have been associated with the development of certain cancers[54]. For example, mutations in the HAT gene CBP have been correlated with the development of certain colorectal and gastric cancers[55], whereas altered HDAC function has been associated with the onset of acute promyelocytic leukemia (APL)[54]. There are several inhibitors of HDACs that show anti-cancer activity in vitro and in vivo[56]. These include the short-chain fatty acids (sodium butyrate, valproic acid (VPA)), the hydroxamic acids (suberoylanilide hydroxamic acid (SAHA), trichostatin A), the cyclic tetrapeptides (depsipeptide (FK-228)) and the benzamides (MS-275). Vorinostat, FK-228, MS-275, and others are currently undergoing early clinical testing.

1.3 Rationale for the Proposed Study

1.3.1 Rationale

Immunotherapy responses have remained limited in ER+ breast cancer. Our preliminary and clinical data suggest that epigenetic priming may be a successful strategy to enhance immune response. However, epigenetic priming is predominantly successful in patients with tumors that have exhausted CD8 subpopulation.

This proposal is focused on the potential role of epigenetic immune priming to reverse therapy resistance in pre- and postmenopausal breast cancer. Initially focused on all hormone therapy

positive patients, data from our pilot study with epigenetic priming suggests that benefits are vastly different if the population is limited to those patients with a 20% or higher expression of CD8 cells with dual expression of PD-L1 and CTLA in tumors (or 10% in blood). The pilot study, therefore, has two objectives,

a) to show that vorinostat can increase the efficacy of pembrolizumab in a select ER+ breast cancer patient population and

b) a biomarker select patient population has a higher than expected response rate to pembrolizumab

The goal of immune priming is to increase the number and composition of tumor-infiltrating lymphocytes, which renders this a relevant approach to therapy resistant ER+ breast cancer. The goal of the biomarker selection is to enrich for a population who is immune responsive

1.3.1.1 Programmed cell death 1 (PD-1) and its ligand PD-L1 in breast cancer

Inhibition of the PD-L1/PD-1 axis has been a major milestone in many cancer types. Clinically, epigenetic immune regulation has been implicated in priming lung cancer cells to PD-1 inhibitors, which resulted in prolonged responses[14,15]. Increased PD-L1 expression has been observed in hormone therapy resistance, frequently reported with loss of progesterone receptor (PR) expression, a measure of hormone therapy resistance[16]. Hence, PD-1 inhibitors may have a role in hormone therapy-resistant breast cancer, and PD-1 inhibitors may be more effective after epigenetic immune priming. Several investigators have shown that HDAC inhibitors have immune modulatory functions, including modulation of Tregs, FoxP3 expression, changes in tumor-infiltrating lymphocytes (TILs), induction of PD-L1 expression, and blockage of PD-1 signaling. Hence, the combination of HDAC inhibitors may potentiate the efficacy of PD-1 inhibitors[17].

1.3.1.2 Pilot Study – Exhausted CD8+ cells predict response to PD-1 therapy in ER+ hormone therapy-resistant breast cancer after epigenetic priming

Our initial pilot study of 34 patients with ER+ positive patients suggests that vorinostat decreases T-reg with Foxp3 expression. However, these effects were only associated with clinical benefit in patients with high expression of CD8 (CTLA/PD-L1) in their blood or tumor samples.

The pilot included 34 patients (median age 56, 88% ECOG 1) who had been treated with a median of 5 (2-12) prior regimens. A minority experienced grade 3-4 toxicity (autoimmune hepatitis, fatigue, thrombocytopenia), with each toxicity occurring in 2 out of 34 patients (6%). Grade 2 toxicities included fatigue (27%), thrombocytopenia (12%), colitis (3%), and pneumonitis (3%). Six patients did not receive Pembrolizumab due to rapid disease progression or toxicity. 18% (5/28) of patients experienced clinical benefit (defined as CR, PR, or stable disease >6 months). Tumor lymphocyte infiltration and PD-L1 expression were low. High expression of PD-1/CTLA-4 dual staining in CD8 cells (>15% in tumor or blood) was seen in 5 patients, with 80% (4/5) of those patients experiencing benefit, and in one other patient who withdrew from the study in week 3 because of immune hepatitis. 95% (21/22) of patients with less than 20% dual expression had no response. Both tumor and peripheral blood CD8 PD-1/CTLA-4 dual expression strongly correlated with time to progression. Furthermore, reduction in Foxp3+/CTLA-4high Treg population in was seen in most tumors treated with vorinostat, but a more significant reduction Foxp3+/CTLA-4high Treg was seen in responding patients.

All patients in the prior study received vorinostat and pembrolizumab, and it is not clear whether the high response rate in the biomarker-enriched group is due to the biomarker expression

alone or the constellation of the presence of the biomarker in the setting of HDAC inhibitor-induced downregulation of Tregs.

Table 1.1 Duration of Response by percentage of dual positivity of PD-1/CTLA-4 (20%)

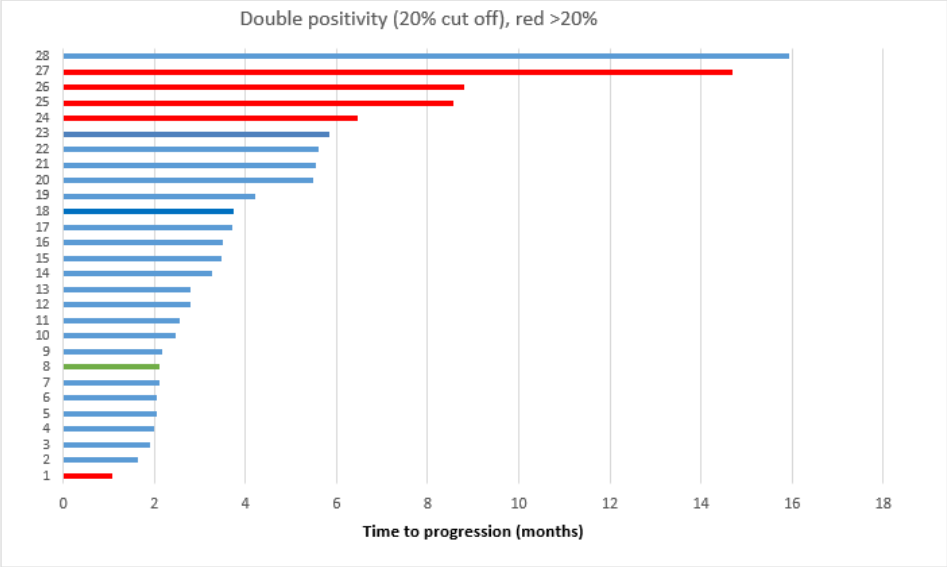
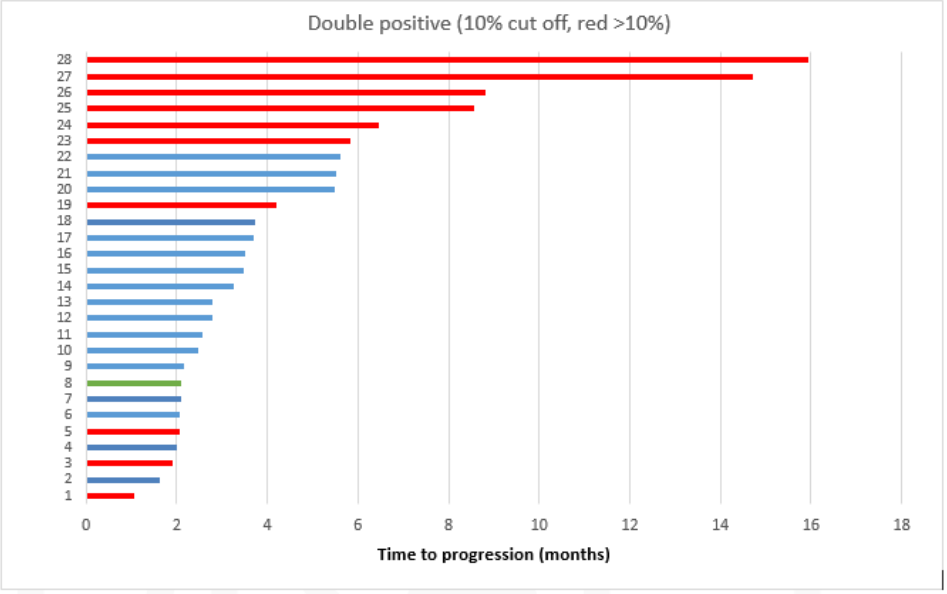


Table 1.2 Duration of Response by percentage of dual positivity of PD-1/CTLA-4 (10%)



1.3.1.3 Prior studies with vorinostat in breast cancer

In a Phase II clinical trial, we evaluated the role of vorinostat (VOR) in reversing hormone therapy resistance in advanced breast cancer[13]. In a single arm study, 43 patients (median age 56 years (31–71)) were treated. A total of 25 patients (58%) received prior adjuvant tamoxifen (TAM), 29 (67%) progressed on at least one prior chemotherapy regimen, 42 (98%) progressed after one, and 23 (54%) after two aromatase inhibitors. The objective response rate by RECIST

criteria was 19%, and the clinical benefit rate (response or stable disease ≥24 weeks) was 40%. The median response duration was 10.3 months (confidence interval: 8.1–12.4). Histone hyperacetylation and higher baseline HDAC2 levels correlated with response and responses were mainly seen in the 56% of patients who had a meaningful change in acetylation with vorinostat. Preclinical studies have further suggested that hormonal therapy must be continued even in the presence of an HDAC inhibitor.

1.3.1.4 Prior studies with other HDAC inhibitors in breast cancer

A second phase II (ENCORE 301) trial evaluated entinostat and exemestane and treated patients with advanced estrogen receptor (ER)-positive breast cancer[57]. This study recently received Breakthrough Therapy designation from the FDA for its potential to reverse resistance to hormonal therapies. The median PFS was 4.3 months versus 2.3 months, for entinostat and placebo, respectively (HR = 0.73; P = 0.06). The median overall survival in the combination arm was 28.1 m compared to 19.8 m in the exemestane arm (HR = 0.59; P = 0.036). The objective response rate to the combination was 6.3%, while to exemestane alone was 4.6% (P = 0.58).

1.4 Rationale for the Dose Selection/Regimen

The rationale and justification for pembrolizumab, vorinostat, and tamoxifen dosing, route of administration, planned maximum dosage, and regimen are as defined in the previously conducted pilot study (NCT02395627)[58].

1.5 Correlative Studies

Immune checkpoint inhibitors have revolutionized cancer therapy, yet have limited efficacy in estrogen receptor (ER+) breast cancer. Implicated factors include scarcity of tumor-infiltrating lymphocytes (TILs), low PD-L1 expression, female gender, and liver involvement. In vitro and in vivo studies suggest that epigenetic modulation with HDAC inhibitors modulate regulatory T cells (Treg) and change TIL composition, which is further associated with the presence of a specific immune signature[58].

Patients with ER+ metastatic breast cancer, who progressed on multiple prior therapies, were treated with tamoxifen in combination with vorinostat and pembrolizumab either immediately or after 3 weeks of epigenetic priming in a phase II trial. Comprehensive flow-cytometric immunophenotyping, PD-L1 staining, and histone acetylation were evaluated on tumor and blood cells[58].

34 patients (median age 56 years (32-81), heavily pretreated with a median of 5 (2-13) prior regimens received at least one dose of vorinostat and evaluable for response. Grade ¾ toxicities in 2 pts each (6%) included immune hepatitis, fatigue, and thrombocytopenia. Grade 2 toxicities were pneumonitis and colitis in 3%, fatigue in 27% and thrombocytopenia in 12% pts. Six patients did not receive pembrolizumab due to rapid progression or toxicity. Clinical benefits rate defined as CR, PR, and stable disease > 6m was seen in 5/28 (18%) of patients. Tumor lymphocyte infiltration and PD-L1 expression were low. High expression of PD-1/CTLA-4 dual staining in CD8 cells of >20% in tumor or blood was seen in 5 patients overall, 4/5 (80%) patients with benefit and in one other patient, who was withdrawn due to immune hepatitis in week 3. Both tumor and peripheral blood CD8 PD-1/CTLA-4 dual expression strongly correlated with time to progression and reduction in $Foxp3^{+}$/CTLA-4^{high} Treg population in tumors by vorinostat[58].

Our data highlight the potential for patient selection based on exhausted CD8+ cells in blood or tumor to predict response to immune checkpoint inhibitors in a small subset of ER+ breast cancer patients (NCT02395627)[58-69].

2 Study Objectives

2.1 Hypothesis

Given the above data, we hypothesize that HDAC induced epigenetic priming in a biomarker enriched study will increase the efficacy of pembrolizumab with patient selection based on exhausted CD8+ cells in blood or tumor in a small subset of (ER)+ breast cancer patients.

Biomarker threshold for exhausted CD8+ will be set at 10% to avoid under-enrollment of patients with potential response.

Response further correlated with exhausted CD4 cells in blood (but not not tumors), thus we will allow enrollment of patients who have dual expression of PD-1 and CTLA4 on CD4 cells in blood only: biomarker threshold will be set at 5%.

Based on the below described earlier study results, we hypothesize that the pembrolizumab and TAM arm even in the setting of biomarker selection will not pass the first stage and will be stopped early after 11 patients and not expanded to 30 patients, whereas the immune priming by vorinostat arm will proceed to the second stage enrolling a total of 35. Under this hypothesis, we will most likely enroll 46 evaluable patients (~65% chance), whereas the possible enrollment ranges from 24 to 65. For the comparison of the treatment arms, the proposed design will have 72.53% power for the Z-test for two proportions conditioning on the study design, when the true response rates are 0.4 and 0.1 for the immune priming and the no immune priming treatment arm.

2.2 Primary Objective and Endpoints

Primary Objective	**Endpoint(s)**	**Time Frame**
To define the role of epigenetic immune priming in a biomarker enriched ER+ breast cancer population on the basis of overall response rate	ORR: CR+PR+SD	From time of initial response to time of progression or death, whichever occurs first, assessed up to 24 weeks

2.3 Secondary Objective(s) and Endpoint(s)

Secondary Objective	**Endpoint(s)**	**Time Frame**
1. To assess duration of response (DOR) 24-week landmark progression-free survival (PFS:24)	DOR (CR+PR)	From initiation of study treatment to time of progression or death, whichever occurs first, assessed up to 24 weeks
2. Median PFS and overall survival (OS)	• Median PFS • overall survival (OS)	From initiation of study treatment to the time of death from any cause on study, assessed up to 48 months
3. Tumor responses will also be calculated by Immune Related Response-Criteria (irRC)	Tumor responses (irRC)	Through study completion, assessed up to 24 months

2.4 Exploratory (Correlative) Objectives

Exploratory Objective	Endpoint(s)
1. Evaluation of biomarker target threshold on response rate (retrospective cut off of 20% vs 10%)	Biomarker target threshold on response rate
2. To assess the ratio of effector T cells: regulatory T cells in blood and tumor biopsies pre- and post-therapy.	Ratio of effector T cells: regulatory T cells in blood and tumor biopsies pre- and post-therapy
3. To evaluate inflammatory T cell signature changes in blood and tumor biopsies pre- and post-therapy.	inflammatory T cell signature changes in blood and tumor biopsies pre- and post-therapy
4. To evaluate changes in number of myeloid-derived suppressor cells (MDSCs) in peripheral blood and tumor biopsies pre- and post-therapy.	changes in number of myeloid-derived suppressor cells (MDSCs) in peripheral blood and tumor biopsies pre- and post-therapy
5. To evaluate changes in histone acetylation in peripheral blood cells and tumor biopsies pre- and post-therapy	changes in histone acetylation in peripheral blood cells and tumor biopsies pre- and post-therapy
6. Initial comparison to vorinostat-induced PD-1 in lymphocytes, PD-L1 modulation	Comparison to vorinostat-induced PD-1 in lymphocytes, PD-L1 modulation
7. Nanostring and 10x sequencing and single cell immune phenotyping (on stored tissue for successful arms only)	Completion of Nanostring and 10x sequencing and single cell immune phenotyping (on stored tissue for successful arms only)
8. Impact of HDAC inhibition of response to pembrolizumab vs. pembrolizumab in biomarker enriched population	Impact of HDAC inhibition

3 Study Design

3.1 Characteristics

We propose a single site Phase II, two-arm, open-label unblinded, 65-patient trial in patients with hormone therapy-resistant breast cancer (HTR) to test the role of epigenetic priming in a biomarker enriched patient population in HTR breast cancer. The two arms include Arm A: pembrolizumab, vorinostat, and tamoxifen and Arm B pembrolizumab and tamoxifen.

Patients will be evaluated for response at 9 weeks (±1 week) by RECIST1.1 (using IR-RECIST) and will continue on therapy if they have stable disease or response at the time of disease evaluations. Patients with progression on imaging but are clinically stable, may stay on study but will require follow-up staging after 4-6 weeks. Patients will be assessed continually for safety and tolerability as well as for any adverse events. If progression on therapy with pembrolizumab, patient may continue if clinically indicated and be re-evaluated after 4-8 weeks.

We will follow AEs of clinical interest as defined by Merck and will dose modify pembrolizumab as per Merck guidelines. We have significant prior experience with vorinostat, tamoxifen, and pembrolizumab combination and are facile with managing drug toxicities.

Tissue biopsies of all patients will be collected prior to enrollment to assess for pre-treatment of our immune signature and PD-L-1 expression. Follow up biopsies and peripheral blood collection will be taken from all patients post-treatment at 8-10 weeks to characterize changes in local tissue effects and antigen-specific cellular and humoral immune responses in peripheral blood.

Patients will be stratified by prior number of hormonal and chemotherapies.

3.2 Sample Size

We adopt a randomized two-arm trial with futility early stopping built-in within each treatment arm using a Simon's two-stage design (Simon, 1989). The effect of vorinostat on pembrolizumab and the effect of pembrolizumab and tamoxifen in this biomarker-selected population of ER+ breast cancer patients will be first tested against the respectively chosen null rate in the first stage within the treatment arms and then compared between the treatment arms.

65 patients to be treated under the study/enrolled in the investigational portion of the study (sample size for primary objective).

For Arm A (vorinostat + TAM + pembro): The null hypothesis that the true response rate for pembrolizumab and vorinostat in ER+ pretreated patients alone without biomarker enrichment is 0.15 which will be tested against the alternative that response rate of pembrolizumab in a biomarker select population is 0.40. In the first stage, 13 patients will be accrued. If there are 2 or fewer responses in these 13 patients, the study will be stopped. Otherwise, 22 additional patients will be accrued for a total of 35. The null hypothesis will be rejected if 10 or more responses are observed in 35 patients. This design yields a type I error rate of 0.025 and power of 0.9 in this treatment arm when the true response rate is 0.4 in this patient subpopulation.

For Arm B (pembro + TAM): The null hypothesis that the true response rate for pembrolizumab in ER+ pretreated patients alone is 0.10 which will be tested against the alternative that response rate of pembrolizumab in a biomarker select population is 0.35. In the first stage, 11 patients will be accrued. If there are 1 or fewer responses in these 11 patients, the study will be stopped. Otherwise, 19 additional patients will be accrued for a total of 30. The null hypothesis will be rejected if 7 or more responses are observed in 30 patients. This design yields a type I error rate of 0.025 and power of 0.9 in this treatment arm when the true response rate of pembro + TAM treatment is 0.35 in this patient subpopulation.

3.3 Eligibility Criteria

Patients must have baseline evaluations performed prior to the first dose of study drug and must meet all inclusion and exclusion criteria. In addition, the patient must be thoroughly informed about all aspects of the study, including the study visit schedule and required evaluations and all regulatory requirements for informed consent. The written informed consent must be obtained from the patient prior to enrollment. The following criteria apply to all patients enrolled in the study unless otherwise specified.

3.3.1 Inclusion Criteria

1. Pre and postmenopausal women or men with stage IV ER+ breast cancer histological or cytological confirmation, 18 years of age or older.

Because no dosing or adverse event data are currently available on the use of pembrolizumab, vorinostat, or tamoxifen in patients <18 years of age, children are excluded from this study but will be eligible for future pediatric trials.

2. >10% expression of PD-1/CTLA-4 dual staining in CD8 cells in tumor or blood or ≥5% expression of PD-1/CTLA-4 dual staining in CD4 in blood (only).
3. Eastern Cooperative Oncology Group (ECOG) Performance Status of ≤ 1.
4. Understand and voluntarily sign an informed consent prior to any study-related assessments or procedures are conducted and are able to adhere to the study visit schedule and other protocol requirements.
5. Consent to paired tumor biopsy
6. Measurable tumor by RECIST criteria
7. Per Good Clinical Practice, any toxicity related to prior therapies that, in the opinion of the investigator, would potentially be worsened with anti-PD1 therapy should be resolved to less than Grade 1
8. Adequate organ function:
    - Absolute neutrophil count (ANC) ≥ 1.5 X 10^9/L
    - Hemoglobin (Hgb) ≥9g/dL (may transfuse if clinically indicated)
    - Platelets (plt) ≥ 100 x 10^9/L
    - Potassium within normal range, or correctable with supplements;
    - AST and ALT ≤ 2.5 x Upper Limit Normal (ULN) or ≤ 5.0 x ULN if liver tumor is present;
    - Serum total bilirubin ≤ 1.5 x ULN
    - Serum creatinine ≤ 1.5 x ULN, or 24-hr clearance ≥ 60ml/min; and
9. Females of childbearing potential (defined as sexually mature women who):
    - Has not undergone a hysterectomy (the surgical removal of the uterus) or bilateral oophorectomy (the surgical removal of both ovaries) or,
    - Has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time during the preceding 24 consecutive months) must have
        - Negative serum pregnancy test within 14days before starting study treatment in females of childbearing potential (FCBP) and willingness to adhere to acceptable forms or birth control (a physician-approved contraceptive method (oral, injectable, or implantable hormonal contraceptive; tubal ligation; intra-uterine device; barrier contraceptive with spermicide; or vasectomized partner)
10. All female and male participants must agree to use approved contraception during the treatment period and for at least 18 weeks after the last dose of study treatment and refrain from donating sperm during this period.

3.3.2 Exclusion Criteria

1. Prior treatment with pembrolizumab or other PD-(L)1
2. Any significant medical condition, laboratory abnormalities, which places the subject at unacceptable risk if he/she were to participate in the study.
3. Has a history of (non-infectious) pneumonitis/interstitial lung disease that required steroids or current pneumonitis/ interstitial lung disease.
4. Has known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected)"
5. Has a history of HBV
6. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the subject's participation for the full duration of the study, or is not in the best interest of the subject to participate, in the opinion of the treating investigator
7. Symptomatic central nervous system metastases. Subjects with brain metastases that have been previously treated and are stable for 6 weeks are allowed.
8. Persistent diarrhea or malabsorption ≥ NCI CTCAE grade 2, despite medical management.
9. Unstable angina, significant cardiac arrhythmia, or New York Heart Association (NYHA) class 3 or 4 congestive heart failure.
10. Prior systemic cancer-directed treatments or investigational modalities ≤ 5 half-lives or 4 weeks, whichever is shorter, prior to starting study drug or who have not recovered from side effects of such therapy (except alopecia).
11. Active autoimmune disease except for vitiligo or hypothyroidism
12. Active and ongoing steroid use, except for non-systemically absorbed treatments (such as inhaled or topical steroid therapy for asthma, COPD, allergic rhinitis).
13. Major surgery ≤ 2 weeks prior to starting a study drug or who have not recovered from side effects of such therapy.
14. Pregnant or breastfeeding.
15. Known Human Immunodeficiency Virus (HIV) infection
16. Known history of tuberculosis
17. Known allergic reaction or intolerability to tamoxifen
18. Patients with prior history of DVTs must be on therapeutic or preventive anticoagulation

3.4 Inclusion and Recruitment of Women and Minorities

Individuals of any sex/gender, race, or ethnicity may participate.

The study recruitment strategy aims to achieve representation of minority groups that reflects the demographics of the affected population in the catchment area.

3.5 Duration of Treatment

Eligible patients will receive treatment as described above, in consecutive 3-week cycles, until progression of disease or unacceptable toxicity. Patients are expected to receive treatment for at least 3 cycles, at which time the first evaluation for efficacy will occur. If there is continued safety and tolerability, treatment may continue.

All patients will be restaged during at 9 weeks (±1 week) and 18 weeks (±1 week) via imaging scans; staging will then be continued every 3 cycles until 6 months. After 6 months, staging may be spaced out to 6 cycles if clinically indicated.

Patients will be followed for evaluation of safety for at least 30 days after the last dose of study drug. Any study drug-related serious adverse events will be followed until resolution, return to baseline grade, or deemed irreversible by the Investigator.

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

3.6 Duration of Follow Up

Patients will be followed for 30 days after end of study participation or removal from study. Patients removed from study for unacceptable treatment-related adverse event(s) will be followed until resolution or stabilization of all treatment-related adverse events to Grade 2 or lower.

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.

Subjects may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn by the investigator or the Sponsor if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding discontinuation or withdrawal are provided in Section 5.4.

3.7 Randomization Procedures

This is an open-label randomized trial; therefore, the sponsor, investigator, and subject will know the treatment administered. Two arms will be tested, with each independent assessment. Patients will be randomized to either arm using a computerized randomization program by Dr. Scott Thomas. Patients will be further stratified by prior number of chemo- and hormonal therapies.

3.8 Primary Completion

The estimated primary completion is 36 months after the study opens to accrual.

3.9 Study Completion

The expected study completion date is 48 months after the study opens to accrual.

The study will conclude when all enrolled patients have been followed for more than 30 days following completion of the study. The estimated duration of study, from start of enrollment to final study report is 4 years.

4 Investigational Products

4.1 Description, Supply, and Storage of Investigational Products

4.1.1 Investigational Product: Pembrolizumab (MK-3475)

Classification

Antineoplastic, Monoclonal antibody (mAb)

Mechanism of Action

Pembrolizumab (previously known as SCH 900475) 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. This blockade enhances functional activity of the target lymphocytes to facilitate tumor regression and ultimately immune rejection.

Metabolism

Pembrolizumab is catalyzed into small peptides and single amino acids via general protein degradation, but it does not rely on metabolism for clearance.

Contraindications

None

Formulation, Appearance, Packaging, and Labeling

Pembrolizumab is supplied as 100 mg/4 mL solution in a single-use vial for intravenous administration. Pembrolizumab is manufactured by Merck. Supplies will be labeled in accordance with regulatory requirements. This trial is open-label; therefore, the participant, 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.

Availability

Pembrolizumab is being obtained as commercial supply provided by Merck.

Storage and handling

Pembrolizumab is stored at the UCSF investigational pharmacy. 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.

Store the diluted solution from the KEYTRUDA 100 mg/4 mL vial either:

- At room temperature for no more than 6 hours from the time of dilution. This includes room temperature storage of the diluted solution and the duration of infusion.

- Under refrigeration at 2°C to 8°C (36°F to 46°F) for no more than 24 hours from the time of dilution. If refrigerated, allow the diluted solution to come to room temperature prior to administration.

Discard after 6 hours at room temperature or after 24 hours under refrigeration.

Do not freeze.

Side Effects

Complete and updated adverse event information is available in the Investigational Drug Brochure (IB) and/or product package insert.

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 participants 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.

4.1.2 Investigational Product: Vorinostat

Classification

Antineoplastic

Mechanism of Action

Vorinostat, a histone deacetylase (HDAC) inhibitor. Histone deacetylases (HDACs) are a family of enzymes that regulate chromatin remodeling and gene transcription via the dynamic process of acetylation and deacetylation of core histones.

Vorinostat, a potent inhibitor of HDAC activity, binds directly to the catalytic pocket of HDAC enzymes. It causes G1 or G2 phase cell-cycle arrest, apoptosis, or differentiation in cultured transformed cells.

Metabolism

The major pathways of vorinostat metabolism involve glucuronidation and hydrolysis, followed by β-oxidation. Human serum levels of two metabolites, O-glucuronide of vorinostat and 4-anilino4-oxobutanoic acid were measured. Both metabolites are pharmacologically inactive. Compared to vorinostat, the mean steady-state serum exposures in humans of the O-glucuronide of vorinostat and 4-anilino-4-oxobutanoic acid were 4-fold and 13-fold higher, respectively. In vitro studies using human liver microsomes indicate negligible biotransformation by cytochromes P450 (CYP).

Contraindications

None

Formulation, Appearance, Packaging, and Labeling

Vorinostat is supplied as size 3 100 mg capsules for oral administration. Vorinostat will be supplied in a 100-120 capsule bottle. Vorinostat will be given at 400 mg per day (4x 100 mg tablets), 4 of 7 days. Vorinostat is manufactured by Merck & Co., Inc.

Availability

Vorinostat is being obtained as commercial supply provided by Merck & Co., Inc.

Storage and handling

Vorinostat is stored at the UCSF investigational pharmacy. Store vorinostat capsules at room temperature, 15 to 30 .C (59 to 86 .F). Do not store above 30.C. Avoid exposure to excessive moisture.

Vorinostat is an anticancer drug. If clean powder is spilled from broken or damaged vorinostat capsules care should be taken to minimize inhalation or direct contact with skin. Wash spill area at least 3 times with ethyl alcohol, followed by water.

Side Effects

Complete and updated adverse event information is available in the current IB and/or product package insert.

4.1.3 Investigational Product: Tamoxifen

Classification

Non-steroidal anti-estrogen

Mechanism of Action

Following a single oral dose of 20 mg tamoxifen, an average peak plasma concentration of 40 ng/mL (range 35 to 45 ng/mL) occurred approximately 5 hours after dosing. The decline in plasma concentrations of tamoxifen is biphasic with a terminal elimination half-life of about 5 to 7 days. The average peak plasma concentration of N-desmethyl tamoxifen is 15 ng/mL (range 10 to 20 ng/mL). Chronic administration of 10 mg tamoxifen given twice daily for 3 months to patients results in average steady-state plasma concentrations of 120 ng/mL (range 67-183 ng/mL) for tamoxifen and 336 ng/mL (range 148-654 ng/mL) for N-desmethyl tamoxifen. The average steady-state plasma concentrations of tamoxifen and N-desmethyl tamoxifen after administration of 20 mg tamoxifen once daily for 3 months are 122 ng/mL (range 71-183 ng/mL) and 353ng/mL (range 152-706 ng/mL), respectively.

After initiation of therapy, steady-state concentrations for tamoxifen are achieved in about 4 weeks, and steady-state concentrations for N-desmethyl tamoxifen are achieved in about 8 weeks, suggesting a half-life of approximately 14 days for this metabolite. In a steady state, crossover study of 10 mg NOLVADEX tablets given twice a day vs. a 20 mg NOLVADEX tablet given once daily, the 20 mg NOLVADEX tablet was bioequivalent to the 10 mg NOLVADEX tablets.

Metabolism

Tamoxifen is extensively metabolized after oral administration. N-desmethyl tamoxifen is the major metabolite found in patients' plasma. The biological activity of N-desmethyl tamoxifen appears to be similar to that of tamoxifen. 4-Hydroxytamoxifen and a side chain primary alcohol derivative of tamoxifen have been identified as minor metabolites in plasma. Tamoxifen is a substrate of cytochrome P-450 3A, 2C9 and 2D6, and an inhibitor of P-glycoprotein.

Excretion:

Studies in women receiving 20 mg of 14C tamoxifen have shown that approximately 65% of the administered dose was excreted from the body over a period of 2 weeks with fecal excretion as the primary route of elimination. The drug is excreted mainly as polar conjugates, with unchanged drug and unconjugated metabolites accounting for less than 30% of the total fecal radioactivity.

Contraindications

Tamoxifen is contraindicated in patients with known hypersensitivity to the drug or any of its ingredients.

Drug-drug Interactions:

In vitro studies showed that erythromycin, cyclosporin, nifedipine, and diltiazem competitively inhibited formation of N-desmethyl tamoxifen with apparent K1 of 20, 1, 45 and 30 μM, respectively. The clinical significance of these in vitro studies is unknown.

Formulation, Appearance, Packaging, and Labeling

Tamoxifen is available in the following doses for oral administration:

- 10 mg Tablets. Each tablet contains 15.2 mg of tamoxifen citrate, which is equivalent to 10 mg of tamoxifen.
- 20 mg Tablets. Each tablet contains 30.4 mg of tamoxifen citrate, which is equivalent to 20 mg of tamoxifen.

The administered dose will be 20 mg daily.

Availability

Tamoxifen is commercially available. It is being obtained as commercial supply.

Storage and handling

Tamoxifen is commercially available. Patients will obtain tamoxifen from their local pharmacy.

Side Effects

Complete and updated adverse event information is available in the current IB and/or product package insert.

4.2 Accountability Records for Investigational Product(s)

UCSF Investigational Drug Services (IDS) will manage drug accountability records for UCSF.

4.3 Ordering Investigational Product(s)

UCSF will obtain pembrolizumab and vorinostat directly from Merck & Co., Inc. Tamoxifen is commercially available.

5 Treatment Plan

5.1 Dosage and Administration

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. Treatment cycle intervals may be increased due to toxicity, as described in Section 5.2. Every effort should be made to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min).

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

Selection of 200 mg as the appropriate dose for a switch to fixed dosing is based on simulation results indicating that 200 mg will provide exposures that are reasonably consistent with those obtained with 2 mg/kg dose and importantly will maintain individual patient exposures within the exposure range established in melanoma as associated with maximal clinical response. A population PK model, which characterized the influence of body weight and other patient covariates on exposure, has been developed using available data from 476 subjects from PN001. The distribution of exposures from the 200 mg fixed dose is predicted to considerably overlap those obtained with the 2 mg/kg dose, with some tendency for individual values to range slightly higher with the 200 mg fixed dose. The slight increase in PK variability predicted for the fixed-dose relative to weight-based dosing is not expected to be clinically important given that the range of individual exposures is well contained within the range of exposures shown in the melanoma studies of 2 and 10 mg/kg to provide similar efficacy and safety. The population PK evaluation revealed that there was no significant impact of tumor burden on exposure. In addition, exposure was similar between the NSCLC and melanoma indications. Therefore, there are no anticipated changes in exposure between different tumor types and indication settings. As vorinostat and tamoxifen are oral, self-administered drugs, drug diaries will be provided for assessing compliance with treatment. The diary will be provided each time vorinostat and tamoxifen are provided to the study participant to take home. Missed doses will be noted and will not be replaced. The participant will proceed with the next scheduled dose at the next scheduled time.

Table 5.1 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

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

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

Table 5.2 Arm A Regimen Description

Investigational Product	Premedication; precautions	Dose	Route	Schedule	Cycle Length
Pembrolizumab	No premedications No precautions	200 mg	Intravenous	Day 1, Week 1 Cycles 1+	3 weeks (21 days)
Vorinostat	Administer whole with food, if possible	400 mg	Oral	Days 4 of 7 days All cycles	
Tamoxifen	No premedications No precautions	20 mg (tablets)	Oral	Daily continuous All cycles	

Table 5.3 Arm B Regimen Description

Investigational Product	Premedication; precautions	Dose	Route	Schedule	Cycle Length
Pembrolizumab	No premedications No precautions	200 mg	Intravenous	Day 1, Week 1 Cycles 1+	3 weeks (21 days)
Tamoxifen	No premedications No precautions	20 mg (tablets)	Oral	Daily continuous All cycles	

Tamoxifen may be omitted in Arm B at the PI's discretion

5.2 Dose Modifications and Dosing Delays

The following dose modification rules will be used with respect to potential toxicity. Toxicity will be assessed according to the NCI CTCAE version 5.0.

The following dose modifications should be made for febrile neutropenia, and blood counts obtained on day one of each cycle. If more than one of these conditions applies, use the most stringent (i.e., the greatest dose reduction). **The AE may be due to pembrolizumab or vorinostat alone in which case the respective agent should be reduced. If overlapping toxicity is suspected, both drugs may be reduced with the potential to re-escalate the non-offending agent. Given the very different nature of pembrolizumab and vorinostat/tamoxifen toxicities, separate tables are shown for individual agents.**

No dose modification will be pursued for tamoxifen.

Hematologic Toxicity*

Adverse Event:* Neutropenia
While dose hold may apply for all days of occurrence, dose modification will only apply if neutropenia persists for day 1, 8, and 15 of each cycle. Dose modifications are not required if labs are drawn on other days and counts have recovered upon retreatment on days 1, 8, 15.

Neutropenia **Febrile neutropenia**	**Management/Next Dose for Vorinostat**
ANC ≥1000	100%
ANC: 500-1000	Hold for until ≤grade 2 #, Restart at 75%: 300 mg qd for all subsequent cycles Second occurrence resume at 200 mg qd for all subsequent cycles Third occurrence: remove from study
ANC: 0-500	Hold for until ≤grade 2 or less# Restart at 75%: 300 mg qd for all subsequent cycles Second occurrence resume at 200 mg qd for all subsequent cycles Third occurrence: discuss with sponsor and principal investigator, consider omitting alternate weeks
#Patient with a dose delay for more than 3 weeks in the first 2 cycles will need to be replaced for toxicity and efficacy assessments.	

Adverse Event: Anemia

Hemoglobin	**Management/Next Dose for Vorinostat**
>8 mg/dl	100 %: 400 mg qd
6.5-8 mg/dl	75 %: 300 mg qd
<6.5 mg/dl	50 %: 200 mg qd
An alternative to dose modification in cases of anemia only would be the use of PRBC transfusion.	

Adverse Event: Thrombocytopenia
While dose hold may apply for all days of occurrence, dose modification will only apply if thrombocytopenia persists for day 1, 8, and 15 of each cycle. Dose modifications are not required if labs are drawn on other days and counts have recovered upon retreatment on days 1, 8, 15.

Platelets	**Management/Next Dose for Vorinostat**
>75’000	100 %: 400 mg qd
≤75’000	100 %: 400 mg qd
≤50’000/mm^3	Hold until ≤grade 2 or less Restart at 75%: 300 mg qd for all subsequent cycles Second occurrence resume at 200 mg qd for all subsequent cycles Third occurrence: discuss with sponsor and principal investigator, consider omitting alternate weeks
≤25’000/mm^3	Hold until ≤grade 2 or less Restart at 75%: 300 mg qd for all subsequent cycles Second occurrence resume at 200 mg qd for all subsequent cycles Third occurrence: remove from study
An alternative to dose modification in cases of anemia only would be the use of PRBC transfusion.	

Adverse Event: Non-hematological toxicities
Laboratory abnormalities must be clinically relevant, and dose and drug-related to prompt dose modifications, in case of uncertainty doses may be re-escalated if toxicities recover.

Bilirubin	**Management/Next Dose for Vorinostat**
≤1.5 mg/dl	100 %: 400 mg qd
1.6 – 3.0 mg/dl	75 %: 300 mg qd
> 3.0 mg/dl	First occurrence: hold until ≤grade 2, 75 %: 300 mg qd Second occurrence: Hold until grade 2 or less, 50 %: 200 mg qd
AST/ALT	**Management/Next Dose for Vorinostat**
≤2.5 x ULN	100 %: 400 mg qd
2.5-5 x ULN	First occurrence: 75 %: 300 mg qd Second occurrence: 50 %: 200 mg qd
> 5 x ULN	First occurrence: hold until ≤grade 2, resume at 75 %: 300 mg qd Second occurrence: Hold until grade 2 or less, 50 %: 200 mg qd Third occurrence: remove from study

Hepatic Dysfunction: Any new increase in LFTs should raise the concern to rule out progressive metastatic disease. If the rise is not due to progressive metastatic disease, give the following dose based on lab values obtained on day 1 of each cycle:

Effects on the liver: Tamoxifen has been associated with changes in liver enzyme levels, and on rare occasions, a spectrum of more severe liver abnormalities including fatty liver, cholestasis, hepatitis, and hepatic necrosis. A few of these serious cases included fatalities. In most reported cases, the relationship to tamoxifen was uncertain. However, some positive rechallenges and dechallenges have been reported. If grade 3 or 4 liver toxicity is maintained after a temporary stopping of vorinostat, both drugs should be stopped. Any rechallenge should be discussed with the study chair. **If treatment is delayed for more than 3 weeks, contact the Principal Investigator.**

Gastrointestinal Toxicity

Nausea/Vomiting/Dehydration: In this protocol, the routine use of any and all anti-emetics is allowed as clinically appropriate; these include the use of dexamethasone and 5-HT3 receptor antagonists.

Patients should maintain adequate fluid and food intake because vorinostat's dose-limiting toxicities are anorexia, dehydration, diarrhea, and fatigue. In the setting of dysgeusia, popsicles and Gatorade have been found to be useful by some investigators to maintain adequate hydration. Patients should also be encouraged to seek a nutritional consult.

Diarrhea: Treat diarrhea promptly with appropriate supportive care, including loperamide. Instruct patients to begin taking loperamide at the first signs of 1) poorly formed or loose stool, 2) occurrence of more bowel movements than usual in one day, or 3) 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. The daily dose should not exceed 16 mg. 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 diarrhea is suspected to be linked to pembrolizumab and is ≥ grade 3, hold dose until toxicity resolves to ≤ grade 1, then resume at dose given in prior cycle.

Other Non-hematological Toxicities:

Laboratory abnormalities must be clinically relevant, and dose and drug-related to prompt dose modifications, in case of uncertainty doses may be re-escalated if toxicities recover

Give the following dose based on the worst toxicity encountered during the previous cycle:

Fatigue	**Management/Next Dose for Vorinostat**
Grade 1	100%
Grade 2	Hold until toxicity is ≤grade 1, then resume at dose given in prior cycle.
Grade 3, 4	Hold until toxicity is ≤ grade 1, then resume at 75% (or less) of dose given in the prior cycle. If grade 3 toxicity recurs despite dose reduction, decrease to 50 % of initial dose.
Other	**Management/Next Dose for Vorinostat**
Grade 1	100%
Grade 2	Hold until toxicity is ≤grade 1, then resume at dose given in prior cycle.
Grade 3	Hold until toxicity is ≤grade 1, then resume at 75% (or less) of dose given in the prior cycle. If grade 3 toxicity recurs despite dose reduction, decrease to 50 % of initial dose.
Grade 4	Discontinue protocol therapy.

Vorinostat may be reduced for grade II fatigue, asthenia, weight loss, or other constitutional symptoms if deemed in the best interest of the patient.

Effects on the Eye: Ocular disturbances, including corneal changes, decrement in color vision perception, retinal vein thrombosis, and retinopathy has been reported in patients receiving tamoxifen. An increased incidence of cataracts and the need for cataract surgery have been reported in patients receiving tamoxifen. If grade 3 or 4 ocular toxicities occur, both drugs should be stopped. Any rechallenge should be discussed with the study chair.

5.2.1 Dose Modifications and Dosing Delays Tables for Specific Adverse Events for Pembrolizumab

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator, including but not limited to the items outlined below:

- Diarrhea: Subjects should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus). In symptomatic subjects, infectious etiologies should be ruled out, and if symptoms are persistent and/or severe, endoscopic evaluation should be considered.
    - In subjects with severe enterocolitis (Grade 3), pembrolizumab will be permanently discontinued, and treatment with systemic corticosteroids should be initiated at a dose of 1 to 2 mg/kg/day of prednisone or equivalent. When symptoms improve to Grade 1 or less, corticosteroid taper should be started and continued over at least 1 month.
    - In subjects with moderate enterocolitis (Grade 2), pembrolizumab should be withheld, and anti-diarrheal treatment should be started. If symptoms are persistent for more than one week, systemic corticosteroids should be initiated (e.g., 0.5 mg/kg/day of prednisone or equivalent). When symptoms improve to Grade 1 or less, corticosteroid taper should be started and continued over at

least 1 month. Regarding guidelines for continuing treatment with pembrolizumab, see Section 5.2.

- All subjects who experience diarrhea should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.

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

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

- Immune-related adverse events: Please see Section 5.2.2 below and the separate guidance document in the administrative binder regarding diagnosis and management of adverse experiences of a potential immunologic etiology. Specific immune-related adverse events (irAEs) will be collected and designated as immune-related events of clinical interest (ECIs) as described in Section 5.2.2

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

AEs associated with pembrolizumab exposure, including coadministration with additional compounds, may represent an immunologic etiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of pembrolizumab/combination treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment are 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. Based on the severity of irAEs, withhold or permanently discontinue pembrolizumab and administer corticosteroids. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab/combination treatment are provided in Table 5.4.

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 Tamoxifen alone, or to pembrolizumab alone, for adverse events listed in Table 5.4, both interventions must be held according to the criteria in Table 5.4 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 5.4.

- If the toxicity does not resolve or the criteria for resuming treatment are not met, the participant must be discontinued from all study interventions.
- If the toxicities do resolve and conditions are aligned with what is defined in Table 5.4, the combination of Vorinostat, Tamoxifen 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 or Tamoxifen alone, re-initiation of pembrolizumab as a monotherapy may be considered at the PI's discretion.

Table 5.4 Dose modification and toxicity management guidelines for immune-related AEs associated with pembrolizumab monotherapy and IO Combinations

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
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
				substituted via IV infusion
AST or ALT Elevation or Increased Bilirubin	Grade 2 [a]	Withhold	• Administer corticosteroids (initial dose of 0.5 to 1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable)
	Grade 3 [b] or 4 [c]	Permanently discontinue	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	
T1DM or Hyperglycemia	New onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold [d]	• Initiate insulin replacement therapy for participants with T1DM • Administer antihyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes
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]		

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

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
	Confirmed SJS, TEN, or DRESS	Permanently discontinue	corticosteroids	or exclude other causes
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 (e.g., vasculitis and sclerosing cholangitis).

5.2.3 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 5.5.

Table 5.5 Pembrolizumab Infusion Reaction Dose modification and Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve, and the participant should be premedicated for the next scheduled dose. **Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment**	Participant may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of analgesic).
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: Epinephrine** IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Oxygen Pressors Corticosteroids Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. **Participant is permanently discontinued from further study drug treatment.**	No subsequent dosing
Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the Common Terminology Criteria for Adverse Events v5.0 (CTCAE) at http://ctep.cancer.gov		

Other allowed dose interruption for pembrolizumab

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

5.2.4 Second Course

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

EITHER

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

OR

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

AND

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

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

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

5.2.5 Monitoring and Toxicity Management

Each patient receiving pembrolizumab in combination with Tamoxifen and Vorinostat will be evaluable for safety. The safety parameters include all laboratory tests and hematological abnormalities, physical findings, and spontaneous reports of adverse events reported to the investigator by patients.

Each patient will be assessed periodically for the development of any toxicity as outlined in Section 6 Study Procedures and Observations. Toxicity will be assessed according to the NCI CTCAE v5.0. Dose adjustments will be made according to the system showing the greatest degree of toxicity.

5.2.5.1 Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be reported to the Sponsor.

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

For the time period beginning at treatment allocation/randomization through 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, any ECI, or follow up to an ECI, whether or not related to the Sponsor's product, must be reported within 24 hours to the Sponsor, either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

Events of Clinical Interest for this trial include:

1. an overdose of Sponsor's product, as defined in Section 7.3.7 - Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor, that is not associated with clinical symptoms or abnormal laboratory results.

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

**Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The trial site guidance for assessment and follow up of these criteria can be found in the Investigator Trial File Binder (or equivalent).*

5.3 Stopping Rules

There is a futility early stopping built-in within each treatment arm. For Arm A (vorinostat + TAM + pembro): In the first stage, 13 patients will be accrued. If there are 2 or fewer responses in these 13 patients, the study will be stopped. For Arm B (pembro and TAM): In the first stage, 11 patients will be accrued. If there are 1 or fewer responses in these 11 patients, the study will be stopped.

Clinical Criteria for Early Trial Termination

1. Early trial termination will be the result of the criteria specified below:
2. Quality or quantity of data recording is inaccurate or incomplete
3. Poor adherence to protocol and regulatory requirements
4. Incidence or severity of adverse drug reaction in this or other studies indicates a potential health hazard to subjects
5. 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 appropriate adjustments to subject treatment can be made.

5.4 Discontinuation and Withdrawal

Participants may discontinue study treatment at any time for any reason or be dropped from the study treatment at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study treatment by the investigator or the Sponsor if study treatment is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding procedures to be performed at study treatment discontinuation are provided in Section 6.3.2.6 – Study Procedures Restaging or Off-Study Visit.

A participant must be discontinued from study treatment but continue to be monitored in the study for any of the following reasons:

- The participant or participant's legally acceptable representative requests to discontinue study treatment
- Confirmed radiographic disease progression outlined in Section 3.5.
- Any progression or recurrence of any malignancy, or any occurrence of another malignancy that requires active treatment
- Unacceptable adverse experiences, as described in Section 7.3.5.
- The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or sponsor, placed the participant at unnecessary risk from continued administration of study treatment.
- The participant has a confirmed positive serum pregnancy test
- Noncompliance with study treatment or procedure requirements
- Recurrent Grade 2 pneumonitis
- Discontinuation of treatment may be considered for participants who have attained a confirmed complete response (CR) and have been treated for at least 8 cycles (at least 24 weeks), receiving [for monotherapy: at least 2 doses of pembrolizumab; for combination treatment: 2 cycles of the combination including 2 doses of pembrolizumab and at least 80% of the planned doses of vorinostat beyond the date when the initial CR was declared. These participants may be eligible for second-course treatment described in Section 5.3.

- The participant is lost to follow-up
- Completion of 35 treatments (approximately 2 years) with pembrolizumab. (Patients may continue vorinostat and tamoxifen.)

Note: The number of treatments is calculated, starting with the first dose. Participants who stop the combination or pembrolizumab after receiving 35 doses may be eligible for retreatment if they progress after stopping study treatment provided they meet the requirements detailed in Section 5.3. Participants may be retreated in the Second Course Phase (Retreatment) for up to an additional 17 cycles (approximately 1 year).

Note to Author:

- *Guidance on duration of pembrolizumab for solid tumors:*
  - *When there is disease present on imaging (i.e., metastatic, locally advanced, bulky disease NOS, etc.) – 24 months of pembrolizumab (35 cycles)*
  - *When there is no disease present on imaging (i.e., adjuvant, following resection, maintenance following induction chemo, etc.) – 12 months of pembrolizumab)*
- *Guidance on duration of pembrolizumab for hematologic malignancies:*
  - *For widespread, recurrent disease – 24 months of pembrolizumab*

When using pembrolizumab as consolidative therapy/ limited disease – 12 months.

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

· The subject or legal representative (such as a parent or legal guardian) withdraws consent.

· Confirmed radiographic disease progression

Note: For unconfirmed radiographic disease progression, but clear clinical progression in the opinion of the treating physician or investigator, the patient should be withdrawn from study for progression.

Note: A subject may be granted an exception to continue on treatment with confirmed radiographic progression if clinically stable or clinically improving by symptoms or tumor markers.

Unacceptable adverse experiences as described in Section 7.3.5

· 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

5.4.1 Supportive Care Guidelines for Pneumonitis

Subjects with symptomatic pneumonitis should immediately stop receiving pembrolizumab and have an evaluation. The evaluation may include bronchoscopy and pulmonary function tests to

rule out other causes such as infection. If the subject is determined to have study drug associated pneumonitis, the suggested treatment plan is detailed in Table 5.6.

Table 5.6 Recommended Approach to Handling Pneumonitis

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

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

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

6 Study Procedures and Schedule of Events

The study-specific procedures and assessments are detailed in this section and outlined in the Study Calendar – Section 6.1.

Screening assessments must be performed within 28 days prior to the first dose of investigational product unless otherwise noted. Any results falling outside of the reference ranges may be repeated at the discretion of the investigator.

All on-study visit procedures are allowed **a window of ± 5 days** unless otherwise noted. Treatment or visit delays for public holidays or weather conditions or patient's personal reasons that do not compromise safety do not constitute a protocol violation. Treatment delays may not exceed 3 weeks unless discussed with the study team for patients with documented benefit. Patients with proven systemic benefit, who have localized progression in the sanctuary site, may receive localized treatment to that site, including but not limited to radiation therapy, gamma knife or surgery.

6.1 Study Calendar

Period/ Procedure	Pre-Screening	Screening[1]	Cycle 1			Cycle 2	Future Cycles[2,3]	Restaging or Off-Study Visit Survival Follow-up
Study Day/Visit Day*	**-365 to -28**	**-28 (±3)**	**1 (±3)**	**10-12 (±3)**	**15 (±3)**	**1 (±3)**	**1 (±3)**	**9 weeks Post Start of Tx (±7)**
Study Treatment/Drug Administration								
Pembrolizumab			200 mg q every 3 weeks; start on C1D1					
Vorinostat			400 mg once a day, 4 days on, 3 days off, weekly every cycle					
Tamoxifen			20 mg once a day continuously					
Administrative Procedures								
Prescreening ICF	X							
Informed consent		X						
Clinical Assessments								
Physical exam		X	X		X	X	X	
Vital signs		X	X		X	X	X	
Performance status		X	X		X	X	X	
Medical history		X						
Concomitant medications		X	X		X	X	X	
Toxicity Assessment[4]		X	X		X	X	X	X[4]
Drug Diaries[5]			X			X	X	
Documentation of Response		X					X	

[1] All screening procedures must be performed within 28 days unless otherwise indicated. Pre-study tests, History and Physical may be used for Day 1 tests if within 2 weeks
[2] Cycle delays up to 14 days for non-medical reason (e.g. holidays) are acceptable without notification of regulatory agencies
[3] Therapy delay for palliative radiation should be based on discussion with the study sponsor and the treating physician, every effort should be made not to hold therapy, patients, where vorinostat is being held for more than 4 weeks, may stay on study if there is felt to be a benefit
[4] Toxicity assessment must be performed until all treatment-related toxicities have been resolved or decreased to grade 1. Adverse events must be recorded up to 30 days after termination on study
[5] Drug diaries will be administered for vorinostat and tamoxifen (oral drugs) only on the first day of every cycle

Period/ Procedure	Pre-Screening	Screening[1]	Cycle 1			Cycle 2	Future Cycles[2,3]	Restaging or Off-Study Visit Survival Follow-up
Study Day/Visit Day*	**-365 to -28**	**-28 (±3)**	**1 (±3)**	**10-12 (±3)**	**15 (±3)**	**1 (±3)**	**1 (±3)**	**9 weeks Post Start of Tx (±7)**
Laboratory Assessments								
Hematology[6]		X	X		X	X	X	
Comprehensive Metabolic Panel[7]		X	X		X	X	X	
Thyroid Function[8]		X				X	X (odd cycles)	
Tumor Markers[9]		X	X			X	X	
Pregnancy test[10]		X					X	
Lymphocyte Subset		X or C1D1[11]		X[12]			X[11] (end of C3)	
PBMC[11]		X or C1D1[11]		X[12]			X[11] (end of C3)	
PK testing		X or C1D1		X			X (end of C3)	
Biomarker testing (prescreening)	X							
Imaging Procedures								
CT/MRI[13]		X					X	X
Tissue Collection/ Biopsy								
Tumor FNA/Biopsy[11]		X or C1D1					X (end of C3)	

[6] Including CBC with differential and platelet count
[7] Sodium, Potassium, Chloride, blood urea nitrogen, Creatinine, Non-fasting glucose, Calcium, ALT, AST, Alkaline Phosphatase, Albumin, Total Bilirubin, Total Protein
[8] Including FT4 and TSH, TSH only for patients on thyroid replacement therapy
[9] CEA, Ca15-3, Ca 125 (if clinically indicated)
[10] For women of childbearing potential, performed within 14 days of starting treatment. Pregnancy test will be repeated if clinically indicated
[11] Correlative studies: Pre-study within 14 days, and end of cycle 3 (preferably day 17-19 while on vorinostat) prior to cycle 4 day 1 pembrolizumab infusion
[12] On day 10-12 pre-dose
[13] Staging studies within 30 days prior to day of start, restaging after cycle 3 (week 9 ±1w), 6 (week 18±1w), then 9, 12, then every 6 cycles if clinically indicated. Partial and complete responses must be confirmed at least one month apart from the first documentation of objective response. Scans may be performed more frequently if clinically indicated
*Note: Window for all study procedures is ±3 days except for scans which is ±7 days

6.2 Schedule of Procedures and Observations

6.2.1 Prescreening Period

- Prescreening ICF
- Laboratory Assessments
    - Biomarkers testing (1 tbsp. blood draw)

6.3 Participant Registration

A written, signed, informed consent form (ICF) and a Health Insurance Portability and Accountability Act (HIPAA) authorization must be obtained before any study-specific assessments are initiated. A copy of the signed ICF will be given to the subject, and a copy will be filed in the medical record. The original will be kept on file with the study records.

All participants consented to the study will be registered in OnCore®, the UCSF Helen Diller Family Comprehensive Cancer Center Clinical Trial Management System (CTMS). The system is password protected and meets HIPAA requirements.

6.3.1 Pretreatment Period

6.3.1.1 Screening Assessments

The Screening procedures and assessments must be completed within 28 days of initiating study treatment.

- Clinical Assessments
    - Documentation of disease assessment (CT scan)
    - Physical examination
    - Vital signs
    - Performance status
    - Complete medical history
    - Concomitant medication review
    - Toxicity assessment
    - Documentation of response
- Laboratory Assessments
    - Hematology labs - CBC with differential and platelet count
    - Comprehensive Metabolic Panel
    - Thyroid function
    - PK testing (or at C1D1)
    - Tumor markers
    - Pregnancy test
    - Lymphocyte Subset (or at C1D1)
    - PBMC (or at C1D1)
- Imaging Procedures

- CT / MRI of breast
- Tumor Tissue Collection
  - Tumor FNA/biopsy (or at C1D1)

6.3.2 Treatment Period

6.3.2.1 Study Procedures, Cycle 1, Day 1

- Study Treatment/Drug Administration
  - Pembrolizumab (200 mg q every 3 weeks)
  - Vorinostat (400 mg once a day, 4 days on, 3 days off, weekly every cycle)
  - Tamoxifen (20 mg once a day continuously)
- Clinical Assessments
  - Physical examination
  - Vital signs
  - Performance status
  - Concomitant medication review
  - Toxicity assessment
  - Drug diaries
- Laboratory Assessments
  - Hematology labs - CBC with differential and platelet count
  - Comprehensive Metabolic Panel
  - PK testing (if not conducted at screening)
  - Tumor markers
  - Lymphocyte Subset (if not conducted at screening)
  - PBMC (if not conducted at screening)
- Tumor Tissue Collection
  - Tumor FNA/biopsy (if not conducted at screening)

6.3.2.2 Study Procedures Cycle 1, Day 10-12

- Study Treatment/Drug Administration
  - Pembrolizumab (200 mg q every 3 weeks)
  - Vorinostat (400 mg once a day, 4 days on, 3 days off, weekly every cycle)
  - Tamoxifen (20 mg once a day continuously)
- Laboratory Assessments
  - PK testing
  - Lymphocyte Subset
  - PBMC

6.3.2.3 Study Procedures Cycle 1, Day 15

- Study Treatment/Drug Administration
  - Pembrolizumab (200 mg q every 3 weeks)
  - Vorinostat (400 mg once a day, 4 days on, 3 days off, weekly every cycle)
  - Tamoxifen (20 mg once a day continuously)
- Clinical Assessments
  - Physical examination
  - Vital signs
  - Performance status
  - Concomitant medication review
  - Toxicity assessment
- Laboratory Assessments
  - Hematology labs - CBC with differential and platelet count
  - Comprehensive Metabolic Panel

6.3.2.4 Study Procedures Cycle 2, Day 1

- Study Treatment/Drug Administration
  - Pembrolizumab (200 mg q every 3 weeks)
  - Vorinostat (400 mg once a day, 4 days on, 3 days off, weekly every cycle)
  - Tamoxifen (20 mg once a day continuously)
- Clinical Assessments
  - Physical examination
  - Vital signs
  - Performance status
  - Concomitant medication review
  - Toxicity assessment
  - Drug diaries
- Laboratory Assessments
  - Hematology labs - CBC with differential and platelet count
  - Comprehensive Metabolic Panel
  - Thyroid function
  - Tumor markers

6.3.2.5 Study Procedures Future Cycles

- Study Treatment/Drug Administration
  - Pembrolizumab (200 mg q every 3 weeks)
  - Vorinostat (400 mg once a day, 4 days on, 3 days off, weekly every cycle)
  - Tamoxifen (20 mg once a day continuously)

- Clinical Assessments
  - Physical examination
  - Vital signs
  - Performance status
  - Concomitant medication review
  - Toxicity assessment
  - Drug diaries
  - Documentation of response
- Laboratory Assessments
  - Hematology labs - CBC with differential and platelet count
  - Comprehensive Metabolic Panel
  - Thyroid function (odd cycles)
  - PK testing (end of C3)
  - Tumor markers
  - Pregnancy test
  - Lymphocyte Subset (end of C3)
  - PBMC (end of C3)
- Imaging Procedures
  - CT / MRI of breast
- Tumor Tissue Collection
  - Tumor FNA/biopsy (end of C3)

6.3.2.6 Study Procedures Restaging or Off-Study Visit

- Study Treatment/Drug Administration
  - Pembrolizumab (200 mg q every 3 weeks)
  - Vorinostat (400 mg once a day, 4 days on, 3 days off, weekly every cycle)
  - Tamoxifen (20 mg once a day continuously)
- Clinical Assessments
  - Toxicity assessment
- Imaging Procedures
  - CT / MRI of breast

6.3.3 Survival Follow-up

After completing the follow-up period, participants will be contacted by telephone every 12 weeks to assess for survival/anti-cancer therapy status until death, withdrawal of consent, or the end of the study, whichever occurs first.

6.4 Correlative Studies

6.4.1 Histone Acetylation in peripheral blood mononuclear cells

Exposure to HDAC inhibitors results in inhibition of histone deacetylation. Histone acetylation (mainly histone H3) has been used as a biological marker of HDAC inhibitor activity. H3 acetylation has been measured successfully in PBMCs in clinical trials using vorinostat and other HDAC inhibitors. We will, therefore, measure H3 and H4 acetylation in peripheral blood mononuclear cells and tumor samples of patients before and after treatment with vorinostat.

Mononuclear cells will be obtained prior to treatment initiation and repeated on day 10 (+2) and at the end of cycle 3 (day 17-19). Cells will be isolated from patient blood by centrifugation at 400 x g (Sorvall, HS4 rotor) for 30 min using a Ficoll-Paque gradient (Sigma, St. Louis, MO) as described by Sandor et al. Histone acetylation will be quantified by WB analysis of PBMCs using an acid extraction method to collect nuclear histone proteins.

6.4.2 Evaluation of vorinostat effects on tumor tissue acetylation and changes in estrogen receptor expression

Post-treatment tumor samples and PBMCs (as well as the vorinostat PK samples) will be obtained on cycle 3 (days 17-19) after the vorinostat morning dose. Fine needle aspirations (FNA) and core biopsies will be obtained either by an interventional radiologist (visceral disease, lymph node) or a cytopathologist (subcutaneous and skin lesions). Diff-Quick air-dry method (FNA) or touch prep analysis (core biopsies) at time of biopsy will be used to confirm the presence of tumor. Tumor samples will be divided and processed for specific techniques as listed below. An attempt for three cores will be made using the appropriate needle. Tissues will be evaluated for the effects of vorinostat on histone acetylation and estrogen expression (by IHC). For IHC, tumors will be fixed in formalin (1 hour/mm thickness), dehydrated, blocked in paraffin. Five-micron sections will be stained with the appropriate antibodies and visualized by light microscopy. Staining will be evaluated using Adobe Photoshop. As the tumor biopsies may contain a mixture of tumor and surrounding cells, cells will be stained (in addition to ER and H3) with specific antibodies used to distinguish tumor versus non-tumor tissues (e.g., cytokeratin (Keratin (5D3)) for breast cancers. PBMCs histone acetylation and ER expression will be quantified by Western blot.

6.4.3 Logistics on Immune modulation

For immune assays we will collect 60cc of blood in green top tubes at baseline and day 10-12 in cycle 1 and on day 17-18 in cycle 3, at the time points specified above for tumor biopsies, FFPE for immune cell infiltrate and a frozen section will be obtained for TCR sequencing.

6.5 Use of Concurrent/Concomitant Medications

6.5.1 Acceptable Concomitant Medications

All treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the case report form (CRF) including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the CRF.

All concomitant medications received within 28 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded. Concomitant medications

administered after 30 days after the last dose of trial treatment should be recorded for SAEs and ECIs as defined in Section 7.3.

Anti-diarrheal and anti-emetic treatment may be given as required, either therapeutically or prophylactically, after such events have occurred in conjunction with a prior dose given without antidiarrheals or anti-emetics. If needed, efforts will be made to standardize such supportive regimens in agreement with participating Investigators.

Other examples of supportive care medications include prophylactic or therapeutic use of erythropoietin for anemia and bisphosphonates (e.g., pamidronate).

6.5.2 Rescue Medications & Supportive Care

Supportive Care Guidelines

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator, including but not limited to the items outlined below:

- Diarrhea: Subjects should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and bowel perforation (such as peritoneal signs and ileus). In symptomatic subjects, infectious etiologies should be ruled out, and if symptoms are persistent and/or severe, endoscopic evaluation should be considered.
    - In subjects with severe enterocolitis (Grade 3), pembrolizumab will be permanently discontinued, and treatment with systemic corticosteroids should be initiated at a dose of 1 to 2 mg/kg/day of prednisone or equivalent. When symptoms improve to Grade 1 or less, corticosteroid taper should be started and continued over at least 1 month.
    - In subjects with moderate enterocolitis (Grade 2), pembrolizumab should be withheld, and anti-diarrheal treatment should be started. If symptoms are persistent for more than one week, systemic corticosteroids should be initiated (e.g., 0.5 mg/kg/day of prednisone or equivalent). When symptoms improve to Grade 1 or less, corticosteroid taper should be started and continued over at least 1 month. Regarding guidelines for continuing treatment with pembrolizumab, see Section 5.2.1.
    - All subjects who experience diarrhea should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
- Nausea/vomiting: Nausea and vomiting should be treated aggressively, and consideration should be given in subsequent cycles to the administration of prophylactic antiemetic therapy according to standard institutional practice. Subjects should be strongly encouraged to maintain liberal oral fluid intake.
- Anti-infectives: Subjects with a documented infectious complication should receive oral or IV antibiotics or other anti-infective agents as considered appropriate by the treating investigator for a given infectious condition, according to standard institutional practice.
- Immune-related adverse events: Please see Section 5.2 below and the separate guidance document in the administrative binder regarding diagnosis and management of adverse experiences of a potential immunologic etiology.

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

Contraception

Pembrolizumab, tamoxifen, and vorinostat may have adverse effects on a fetus in utero. Furthermore, it is not known if pembrolizumab has transient adverse effects on the composition of sperm. 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, 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. The two birth control methods can be either two barrier methods or a barrier method plus a hormonal method to prevent pregnancy. Subjects should start using birth control from study visit 1 throughout the study period up to 120 days after the last dose of study therapy.

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

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study, they must adhere to the contraception requirement (described above) for the duration of the study and during the follow-up period defined in Section 7.3.9 - Reporting of Pregnancy and Lactation to the regulatory agencies and Merck. If there is any question that a subject will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

6.6 Prohibited 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:

- Anti-cancer systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than Pembrolizumab
- Radiation therapy

  - Note: Radiation therapy to a symptomatic solitary lesion or the brain may be allowed after consultation with the study PI and Merck.

- 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, chicken pox, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines and are not allowed.

- Glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the study PI and Merck.

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.

7 Reporting and Documentation of Results

7.1 Evaluation of Efficacy: Antitumor Effect – Solid Tumors

Response and progression in this study will be evaluated using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1)[70]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST v1.1 criteria.

7.1.1 Definitions

Evaluable for toxicity

All participants will be evaluable for toxicity from the time of their first treatment with pembrolizumab, vorinostat, and tamoxifen.

Evaluable for objective response

Only those participants who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These participants will have their response classified according to the definitions stated below. (Note: Participations who exhibit objective disease progression prior to the end of Cycle 1 will also be considered evaluable.)

Evaluable Non-Target Disease Response

Participants who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

7.1.2 Disease Parameters

Measurable disease

Measurable disease is defined as lesions (or tumors) that can be accurately measured in at least one dimension (longest diameter to be recorded) with a minimum size of 10mm by CT scan (irrespective of scanner type) and MRI (no less than double the slice thickness and a minimum of 10mm), 10mm caliper measurement by clinical exam (when superficial), and/or 20mm by chest X-ray (if clearly defined and surrounded by aerated lung).

All tumor measurements will be recorded in millimeters or decimal fractions of centimeters. Previously irradiated lesions are considered non-measurable except in cases of documented progression of the lesion since the completion of radiation therapy.

Malignant lymph nodes

To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm (≥1.5 cm) in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm [0.5 cm]). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease (Tumor Markers)

All other lesions (or sites of disease), including small lesions (longest diameter <10 mm [<1 cm] or pathological lymph nodes with ≥10 to <15 mm [≥1 to <1.5 cm] short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Target lesions

All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition, should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters

will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions

All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as non-target lesions and should also be recorded at baseline. It is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (e.g. “multiple enlarged pelvic lymph nodes” or “multiple liver metastases”). Bone lesions may be measurable if ≥ 1 cm on MRI. Measurements of these lesions are not required, but the presence or absence of each will be noted throughout follow-up.

Non-measurable disease (Tumor Markers)

Non-measurable disease is all other lesions (or sites of disease), including small lesions (longest diameter < 20 mm with conventional techniques or < 10 mm using spiral CT scan). Leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques are all non-measurable (e.g., PSA, CA-125, CA19-9, CEA).

7.1.3 Methods for Evaluation of Measurable Disease

All measurements will be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations will be performed as closely as possible to the beginning of treatment and never more than 28 days before the beginning of the treatment.

The same method of assessment and the same technique will be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥10 mm (≥1 cm) diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm (0.5 cm) or less. If CT scans have slice thickness greater than 5 mm (0.5 cm), the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g., for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline, and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should

be used, and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

7.1.4 Response Criteria

Evaluation of Target Lesions

Complete Response (CR)

Disappearance of all target lesions, determined by two separate observations conducted not less than 4 weeks apart. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm (the sum may not be “0” if there are target nodes). There can be no appearance of new lesions.

Partial Response (PR)

At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD. There can be no appearance of new lesions.

Progressive Disease (PD)

At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm (0.5 cm). (Note: the appearance of one or more new lesions is also considered progressions).

Stable Disease (SD)

Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started.

Evaluation of Non-Target Lesions

Complete Response (CR)

Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Incomplete Response/Stable Disease (SD)

Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD)

Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions.

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The participant’s best response assignment will depend on the achievement of both measurement and confirmation criteria.

Table 7.1 Response Criteria for Participants with Measurable Disease (*i.e.*, Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.
Note: Participants with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration."* Every effort should be made to document the objective progression even after discontinuation of treatment.

Table 7.2 Response Criteria for Participants with Non-Measurable Disease (*i.e.*, Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised

Duration of Response

Duration of overall response

The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Duration of stable disease

Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

Progression-Free Survival

Progression-free survival (PFS) is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first.

7.2 Evaluation of Safety

The safety parameters for this study include all laboratory tests and hematological abnormalities, physical findings, and spontaneous reports of adverse events reported to the investigator by participants.

Toxicity will be assessed according to the NCI CTCAE version 5.0. Safety analyses will be performed for all participants who have received at least one dose of study drug.

7.3 Definitions of Adverse Events

7.3.1 Adverse Event

An adverse event (also known as an adverse experience) is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug-related. More specifically, an adverse event (can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, without any judgment about causality. An adverse event can arise from any use of the drug (e.g., off-label use, use in combination with another drug) and from any route of administration, formulation, or dose, including an overdose.

7.3.2 Adverse Reaction

An adverse reaction is defined as any adverse event caused by the use of a drug. Adverse reactions are a subset of all suspected adverse reactions for which there is reason to conclude that the drug caused the event.

7.3.3 Suspected Adverse Reaction

A suspected adverse reaction is defined as any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, “reasonable possibility” indicates that there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than an adverse reaction.

7.3.3.1 Unexpected

An adverse event or suspected adverse reaction is considered *unexpected* if it is not listed in the investigator brochure or package insert(s), or is not listed at the specificity or severity that has been observed, or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application.

“Unexpected,” as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or

as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

Adverse events that would be anticipated to occur as part of the disease process are considered *unexpected* for the purposes of reporting because they would not be listed in the investigator brochure. For example, a certain number of non-acute deaths in a cancer trial would be anticipated as an outcome of the underlying disease, but such deaths would generally not be listed as a suspected adverse reaction in the investigator brochure.

Some adverse events are listed in the Investigator Brochure as occurring with the same class of drugs, or as anticipated from the pharmacological properties of the drug, even though they have not been observed with the drug under investigation. Such events would be considered *unexpected* until they have been observed with the drug under investigation. For example, although angioedema is anticipated to occur in some participants exposed to drugs in the angiotensin-converting enzyme inhibitor class and angioedema would be described in the investigator brochure as a class effect, the first case of angioedema observed with the drug under investigation should be considered *unexpected* for reporting purposes.

7.3.3.2 Serious

An adverse event or suspected adverse reaction is considered *serious* if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death
- Life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life function
- Congenital anomaly/birth defect

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

<u>Serious Adverse Events</u>

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

- Results in death;
- Is life-threatening;
- Results in persistent or significant disability/incapacity;
- Results in or prolongs an existing inpatient hospitalization;
- Is a congenital anomaly/birth defect;
- Is a new cancer (that is not a condition of the study);

- Is associated with an overdose;
- Is another important medical event

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

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

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

Any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study that occurs to any subject from the time the consent is signed through 30 days following cessation of treatment, or the initiation of new anti-cancer therapy, whichever is earlier, whether or not related to Merck product, must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety.

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

Additionally, any serious adverse event, considered by an investigator who is a qualified physician to be related to Merck product that is brought to the attention of the investigator at any time outside of the time period specified in the previous paragraph also must be reported immediately to the Sponsor and Merck.

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

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

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

7.3.3.3 Life-threatening

An adverse event or suspected adverse reaction is considered life-threatening if, in the view of either the investigator or sponsor, its occurrence places the participant at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

7.3.4 Recording of Adverse Events

Refer to the Data Safety Monitoring Plan, located in Appendix 2.

7.3.5 Follow-up of Adverse Events

All participants who experience adverse events will be followed with appropriate medical management until resolved or stabilized, as determined by the investigator, or until the initiation of new anti-cancer therapy, whichever occurs first. For selected adverse events for which administration of the investigational product was stopped, a re-challenge of the subject with the investigational drug may be conducted if considered both safe and ethical by the investigator.

7.3.6 Adverse Events Reporting

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

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

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

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

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

- All AEs from the time of treatment allocation/randomization through 30 days following cessation of study treatment must be reported by the investigator.
- All AEs meeting serious criteria, from the time of treatment allocation/randomization through 90 days following cessation of study treatment, or 30 days following cessation of study treatment if the participant initiates new anticancer therapy, whichever is earlier must be reported by the investigator.
- All pregnancies and exposure during breastfeeding, from the time of treatment allocation/randomization through 120 days following cessation of study treatment, or 30 days following cessation of study treatment if the participant initiates new anticancer therapy must be reported by the investigator.

- Additionally, any SAE brought to the attention of an investigator at any time outside of the time period specified above must be reported immediately by the investigator if the event is considered to be drug-related.

Investigators are not obligated to actively seek AE or SAE or other reportable safety events in former study participants. However, if the investigator learns of any SAE, including death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify Merck.

All adverse events, whether or not unexpected, and whether or not considered to be associated with the use of the study drug, will be entered into OnCore®, as noted above.

The Investigator will assess all adverse events and determine reportability requirements to the UCSF Data and Safety Monitoring Committee (DSMC) and UCSF's Institutional Review Board (IRB); and, when the study is conducted under an Investigational New Drug Application (IND), to the Food and Drug Administration (FDA) if it meets the FDA reporting criteria.

All adverse events entered into OnCore® will be reviewed by the Helen Diller Family Comprehensive Cancer Center Site Committee on a weekly basis. The Site Committee will review and discuss at each weekly meeting the selected toxicity, the toxicity grade, and the attribution of relationship of the adverse event to the administration of the study drug(s).

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

In addition, all suspected adverse reactions considered "serious" entered into OnCore® will be reviewed and monitored by the Data and Safety Monitoring Committee on an ongoing basis and discussed at DSMC meetings, which take place every six weeks.

For a detailed description of the Data and Safety Monitoring Plan for a Phase 2 or 3 Institutional Study at the Helen Diller Comprehensive Cancer Center, please refer to Appendix 2.

7.3.7 Definition of an Overdose for this Protocol and Reporting of Overdose to the Study PI and Merck

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

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

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

All reports of overdose with and without an adverse event must be reported within 24 hours to the Sponsor and within 2 working days hours to Merck Global Safety. [redacted]

7.3.7.1 Event of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be reported within 2 working days to Merck Global Safety. [redacted]

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

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

Events of clinical interest for this trial include:

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

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

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

7.3.8 Adverse Events Monitoring

Refer to the Data Safety Monitoring Plan, located in Appendix 2.

7.3.9 Expedited Reporting

Reporting to the Data and Safety Monitoring Committee

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

Reporting to Institutional Review Board

The UCSF PI must report events to the UCSF IRB according to institutional guidelines.

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

Reporting to Sponsor – Merck & Co

Any serious adverse event, that are unexpected and related, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study that occurs to any subject from the time the consent is signed through 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, whether or not related to the Sponsor's product, must be reported within 24 hours to the Sponsor either by electronic media or paper. Sponsor Contact information can be found in the Investigator Trial File Binder (or equivalent).

Additionally, any serious adverse event, considered by an investigator who is a qualified physician to be related to the Sponsor's product that is brought to the attention of the investigator at any time outside of the time period specified in the previous paragraph also must be reported immediately to the Sponsor.

Expedited Reporting to the FDA

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

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

- Suspected adverse reaction
- Unexpected
- Serious

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

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

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

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

Reporting to Industry Partners

Reporting of Pregnancy and Lactation to the Sponsor and Merck

Although pregnancy and infant exposure during breastfeeding are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a participant (spontaneously reported to them) that occurs during the study.

Pregnancies and infant exposures during breastfeeding that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the participant to be excluded from the trial, or are the result of a protocol-specified

intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

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

Such events must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety. [redacted]

8 Statistical Considerations and Evaluation of Results

This is a randomized two-arm trial with futility early stopping built-in within each treatment arm using a Simon's two-stage design[71] (Simon, 1989). The effect of vorinostat on pembrolizumab and the effect of pembrolizumab and tamoxifen in this biomarker-selected population of ER+ breast cancer patients will be first tested against the respectively chosen null rate in the first stage within the treatment arms and then compared between the treatment arms.

8.1 Sample Size Considerations

8.1.1 Sample Size and Power Estimate

For Arm A (pembro + vorinostat + TAM): The null hypothesis that the true response rate for pembrolizumab and vorinostat in ER+ pretreated patients alone without biomarker enrichment is 0.15 which will be tested against the alternative that response rate of pembrolizumab in a biomarker select population is 0.40. In the first stage, 13 patients will be accrued. If there are 2 or fewer responses in these 13 patients, the study will be stopped. Otherwise, 22 additional patients will be accrued for a total of 35. The null hypothesis will be rejected if 10 or more responses are observed in 35 patients. This design yields a type I error rate of 0.025 and power of 0.9 in this treatment arm when the true response rate is 0.4 in this patient subpopulation.

For Arm B (pembro + TAM): The null hypothesis that the true response rate for pembrolizumab in ER+ pretreated patients alone is 0.10 which will be tested against the alternative that response rate of pembrolizumab in a biomarker select population is 0.35. In the first stage, 11 patients will be accrued. If there are 1 or fewer responses in these 11 patients, the study will be stopped. Otherwise, 19 additional patients will be accrued for a total of 30. The null hypothesis will be rejected if 7 or more responses are observed in 30 patients. This design yields a type I error rate of 0.025 and power of 0.9 in this treatment arm when the true response rate of pembro and TAM treatment is 0.35 in this patient subpopulation.

Based on earlier results in Section 1.3 and hypothesized treatment effects, we will most likely to enroll 46 evaluable patients (~65% chance), whereas the possible enrollment ranges from 24 to 65. For the comparison of the treatment arms, the proposed design will have 72.53% power for the Fisher's exact test at 0.1 significance level when the true response rates are 0.4 and 0.1 for the immune priming and the no immune priming treatment arm.

8.1.2 Randomization

This is an open-label randomized trial; therefore, the sponsor, investigator, and subject will know the treatment administered. Two arms will be tested, with each independent assessment. Patients will be randomized to either arm using a computerized randomization program by Dr. Mi-Ok Kim.

8.1.3 Stratification Factors

Patients will be stratified by prior number of chemo- and hormonal therapies.

8.1.4 Accrual Estimates

Ten patients are expected to be eligible yearly based on prior accrual for a similar population.

8.2 Interim Analyses and Stopping Rules

This is a randomized two-arm trial with futility early stopping built-in within each treatment arm using a Simon's two-stage design[71].

In addition to the interim analysis for efficacy that is built into the Simon 2-stage design (see above), in each arm, we will evaluate the need for dose modification after 6 patients have been enrolled. If 2 or more patients have a grade 3 non-hematologic toxicity that is clearly related to pembrolizumab, this agent will be reduced to 75%. Dose modification of vorinostat should be undertaken as per dose modification guidelines, a prior study with vorinostat and tamoxifen suggest that there is a high interpatient variability and tolerance and vorinostat will be adjusted per dose modification guidelines individually.

8.3 Analyses Plans

8.3.1 Analysis Population

We will conduct an intention-to-treat analysis of efficacy. All randomized patients will be evaluated.

For evaluation of safety, we will restrict the arm-specific samples to all patients who have received at least one dose of investigational therapy.

8.3.2 Primary Analysis (or Analysis of Primary Endpoints)

Primary Endpoint 1 Analysis (Evaluation of Efficacy)

For each arm objective response rate (ORR) will be defined as the proportion of participants randomized to that arm whose status is SD or better (CR, PR) at 24 weeks' follow-up. Within each treatment arm, the observed ORR will be compared to the respective null (ineffective) rate using the decision rule provided by the Simon's two-stage design. In addition to calculating the ORR, we will calculate the corresponding one-sided 95% confidence interval by appropriately accounting for the Simon's two-stage design: given the observed response number (s), testing of the null hypothesis of H0:p≤p0 will reject the null if the probability of observing as many or less than the observed number of responses (s) is less than the significance level: Prob(S≤s | p0)<α. Using this hypothesis inversely, we can construct a (1-α)100% one-sided confidence interval is given as a set

$$\{p{:}Prob(S \leq s \,|\, p0 = p) < \alpha\}$$

where Prob(S≤s ⏐ p0=p)indicates the joint distribution of stage to stop and observed response number (s) as in Chang et al., 1989[72]. Similarly, the observed rates will be compared between the treatment arms using the Z-test and appropriately accounting for the Simon's two-stage design.

8.3.3 Secondary Analysis (or Analysis of Secondary Endpoints)

We will use median (DOR, OS, PFS, computed by the Kaplan-Meier estimator) and percentages (% irRC) to summarize secondary endpoints. The respective confidence intervals will be computed as well.

8.3.4 Exploratory/Correlative Analysis/Assessments

8.3.4.1 Analysis of Tissue-based Endpoints

Note: Tissue will be used for multiple different exploratory assays. In the event that there is insufficient tissue to perform all assays for an individual subject, the tissue should be prioritized for assays as follows, in which the first assay described is the highest priority.

Tumor PD-L1 Assessment

PD-L1 protein expression on tumor tissue from pre-treatment and post-Cycle-3 biopsies and any other tumor biospecimens obtained will be evaluated immunohistochemically and scored on a scale of 0, 1, 2, or 3. This scoring will be used for the determination of relationships between tumor PD-L1 expression and clinical responses described above. Specifically, in addition to hypothesizing that delayed pembrolizumab treatment (i.e., Arm A) will increase tumor response, we hypothesize that (i) PD-L1 expression will stimulate tumor response, (ii) but will not be associated with treatment (because PD-L1 is stimulated by vorinostat, not pembrolizumab).

For analysis, PD-L1 expression level, scored as {0,1,2,3}, will be classified as binary (0 =negative; 1-3 =positive); across two time-points, this defines four types of PD-L1 participants: {0,0; 0,1; 1,0; 1,1}. We will use logistic regression to estimate Cycle-6 tumor response rate (95% CI) as a function of study arm and PD-L1 level at baseline and Cycle 3. Either time-point will be eliminated from the model if its effect is weak (p>0.2), leaving two types of PD-L1 participants: either {0,0; 1;1} or {0,0; 0,1}.

Tissue Immune Subset Quantification and Localization

For all subjects, immune cell subsets and localization will be summarized by changes from baseline to after treatment using descriptive statistics.

Immune Cell mRNA Signatures of Response

To identify individual genes whose expression levels at pre-treatment are associated with pCR, we will apply two-sample t-tests to compare responders and non-responders. Adjusted P values controlling for false discovery rate (Benjamini and Hochberg method) will be derived. In addition, to assess association of pre-specified immune gene signature with response, the median expression level of the component genes will be used to represent the signature and two-sample t-tests will be used. For genes or signatures that emerge as significantly associated with response, logistic regression models will be used to assess their independent association with response after adjusting for known clinical prognostic factors. To identify pharmacodynamic markers, paired t-test will be carried out to examine immune gene expression differences between pre-treatment and post-treatment samples. Additionally, association of gene expression levels after epigenetic priming with long-term efficacy outcomes, such as PFS and

DFS, will be explored using the Cox proportional hazards regression model. Hierarchical clustering superimposed with response status, relevant baseline or prognostic characteristics or experimental factors will be performed using Spearman correlation and complete linkage to visualize the discriminating power of the immune gene expression and the correlative structure among the genes and the samples.

T cell Receptor (TCR) Deep Sequencing

The change in tumor-infiltrating TCR between pre-treatment and post-epigenetic priming will be assessed by calculating the number of unique clonotypes comprising the top 25th percentile of cumulative reads after sorting by clone abundance. Repertoire change between sequencing experiments will be measured using Morisita's distance. This analysis will also be performed in subjects receiving adjuvant chemotherapy using the same statistical techniques to evaluate the impact of adjuvant MPDL3280A on circulating T cell repertoire remodeling.

Genomic Signatures of Response

It is hypothesized that tumors with highly mutated or copy-aberrant genomes will either overexpress native proteins or express novel mutant proteins, both of which may be recognized by the immune system and serve as tumor-specific antigens. Therefore, the effect of genomic mutations on the immune landscape will be investigated in each of the cohorts in this study as follows.

Tumor DNA will be isolated from pre-treatment tissue and post-epigenetic priming specimens and will be analyzed for copy number using the Human Genome CGH 244K Microarray (Agilent, Santa Clara, CA) and/or by next-generation sequencing. Results will be analyzed with DNA Analytics software (Agilent) and with the assistance of the UCSF Genome Core and the UCSF Biostatistics core. For copy number paired Wilcoxon signed-rank test will be applied to test the difference of tumor gene copy number between pre and post-treatment. Two-sample Wilcoxon signed-rank test will be used to test the gene copy number between tumor responders and non-responders for pre-treatment, post-treatment, and changes before and after the treatment, separately. Multiple testing adjustment will be done by controlling false positive rate. Next-generation sequencing will take place using appropriate methods and biostatistical analyses. Annotation will be based on NCBI and UCSC databases. Chi-square test will be applied to obtain the significant variants associated with the clinical response.

8.3.4.2 Analysis of Immune Endpoints

Immune Cell Activation

For each arm individually, flow cytometry of circulating immune cell subsets will also be performed on pre-treatment blood and again after 9 weeks on vorinostat (post epigenetic priming). Established flow cytometry panels will examine T cell activation. Immune cell quantification will be summarized by changes from baseline to after treatment using descriptive statistics. Furthermore, paired Wilcox on signed-rank test will be applied to test the pre-post treatment changes. When available, immune cells digested from resected tumor tissues will also be assessed by flow cytometry.

Circulating Antibody Detection and Characterization

Spotted antigen arrays will be used to detect circulating antibodies will be performed on sera derived from the pretreatment and after 9 weeks on vorinostat. After standard preprocessing of the protein array data, Cluster and Treeview software will be used for unsupervised clustering of the data with Pearson correlation and complete linkage. For each array, an antigen is identified

as being detected if its value is above the median. To determine the number of up- and down-modulated antibodies, the difference in log2 intensity values of pretreatment and post-treatment samples will be taken for each patient to identify antigens that are detected differentially due to treatment. Number of antibodies with at least 2- or 4-fold difference between pretreatment and post-treatment samples will be compared between clinical responders and nonresponders by performing two-sided Wilcoxon rank sum test.

All correlative studies and assays will be performed in the Munster lab, in conjunction with Merck, with the help of Dr. Lawrence Fong and other experts in the field.

9 Study Management

9.1 Pre-study Documentation

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

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

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

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

9.2 Institutional Review Board Approval

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

9.3 Informed Consent

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

9.4 Changes in the Protocol

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

If it becomes necessary to alter the protocol to eliminate an immediate hazard to participants, an amendment may be implemented prior to IRB approval. In this circumstance, however, the PI must then notify the IRB according to institutional requirements.

9.5 Handling and Documentation of Clinical Supplies

The PI will maintain complete records showing the receipt, dispensation, return, or other disposition of all investigational drugs at the site. The date, quantity, and batch or code number of the drug, and the identification of participants to whom the investigational product has been dispensed by participant number and initials will be included.

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

9.6 Case Report Forms (CRFs)

The PI and/or designee will prepare and maintain adequate and accurate participant case histories with observations and data pertinent to the study. Study-specific Case Report Forms (CRFs) will document safety and treatment outcomes for safety monitoring and data analysis. All study data will be entered into OnCore® via standardized CRFs in accordance with the CTMS study calendar, using single data entry with a secure access account. Study personnel will complete the CRFs; the PI will review and approve the completed CRFs.

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

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

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

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

9.7 Oversight and Monitoring Plan

The UCSF Helen Diller Family Comprehensive Cancer Center DSMC will be the monitoring entity for this study. The UCSF DSMC will monitor the study in accordance with the NCI-approved Data and Safety Monitoring Plan (DSMP). The DSMC will routinely review all adverse events and suspected adverse reactions considered "serious." The DSMC will audit study-related activities to ensure that the study is conducted in accordance with the protocol, local

standard operating procedures, FDA regulations, and Good Clinical Practice (GCP). Significant results of the DSMC audit will be communicated to the IRB and the appropriate regulatory authorities at the time of continuing review, or in an expedited fashion, as applicable. See Appendix 2 - Data and Safety Monitoring Plan.

9.8 Record Keeping and Record Retention

The PI is required to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects, as well as written records of the disposition of the drug when the study ends.

The PI is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation. Case histories include the case report forms and supporting data including, for example, signed and dated consent forms and medical records including, for example, progress notes of the physician, the individual's hospital chart(s), and the nurses' notes. The case history for each individual shall document that informed consent was obtained prior to participation in the study.

Study documentation includes all CRFs, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed participant consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

In accordance with FDA regulations, the PI shall retain records for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified.

10 References

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Appendix 1 Performance Status Criteria

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Descriptions	Percent	Description
0	Normal activity Fully active, able to carry on all pre-disease performance without restriction	100	Normal, no complaints, no evidence of disease
		90	Able to carry on normal activity; minor signs or symptoms of disease
1	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)	80	Normal activity with effort; some signs or symptoms of disease
		70	Cares for self, unable to carry on normal activity or to do active 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	60	Requires occasional assistance, but is able to care for most of his/her needs
		50	Requires considerable assistance and frequent medical care
3	In bed > 50% of the time Capable of only limited self-care, confined to bed or chair more than 50% of waking hours	40	Disabled, requires special care and assistance
		30	Severely disabled, hospitalization indicated Death not imminent
4	100% bedridden Completely disabled Cannot carry on any self-care Totally confined to bed or chair	20	Very sick, hospitalization indicated Death not imminent
		10	Moribund, fatal processes progressing rapidly
5	Dead	0	Dead

Appendix 2 Data and Safety Monitoring Plan for a Phase II or III Institutional Study

Data and Safety Monitoring Plan for a Phase II or III Institutional Trial

1. Oversight and Monitoring Plan

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

- Semiannual auditing (depending on trial accrual)
- Review of serious adverse events
- Minimum of biennial regulatory auditing

2. Monitoring and Reporting Guidelines

Investigators will conduct a continuous review of data and participant safety at monthly site committee meetings where the results of each participant's treatment are discussed and documented in the site committee minutes.

All institutional Phase II and III therapeutic trials are audited on a semiannual basis, with all data from twenty percent of the enrolled participants audited by the DSMC Monitor/Auditor. The assigned DSMC Monitor/Auditor will review no more than a total of 10 participant charts during the course of auditing this trial. DSMC Monitor/Auditors will send a follow-up report to the study team within 20 business days after the auditing visit is complete for the PI and the study team to resolve all action items from this report within 20 business days. An abbreviated regulatory review (i.e., reviewing protocol and consent versions, SAEs, PVs, DOA logs, 1572 forms, etc.) will occur at each participant monitoring review; however, a full regulatory review will occur on a biennially basis by the DSMC for regulatory compliance.

Auditing of all enrolled participants in these trials will be complete after 20% of enrolled participants have been audited through five cycles of treatment. However, regulatory reviews of the trial, safety reviews (i.e., Serious Adverse Event (SAE) reviews and Protocol Violation (PV) reviews), and audit/inspection preparation (as applicable) will continue until the trial is closed by the IRB.

3. Review and Oversight Requirements

3.1 Adverse Event Monitoring

All Grade 3-5 adverse events (AEs), whether or not considered to be expected or unexpected and whether or not considered to be associated with the use of the

investigational agent(s) or study procedure, will be entered into OnCore®, UCSF's Clinical Trial Management System.

Adverse events are graded according to the Common Terminology Criteria for Adverse Events (CTCAE) as developed and revised by the Common Therapy Evaluation Program (CTEP) of the National Cancer Institute. Adverse events are further given an assignment of attribution or relationship to investigational agent or study procedure. Attribution categories are:

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

All Grade 3-5 adverse events entered into OnCore® will be reviewed on a monthly basis at the Site Committee meetings. The Site Committee will review and discuss the selected toxicity, the toxicity grade, and attribution assignment.

3.2 Serious Adverse Event Reporting

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

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

Serious adverse event reporting will be in accordance with all IRB regulations. For trials conducted under an investigational new drug (IND) application, the SAE will be reported in accordance with Code of Federal Regulation Title 21 Part 312.32 and will be reported on a Med Watch form.

UCSF IRB website for guidance in reporting serious adverse events:

https://irb.ucsf.edu/adverse-event

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

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

If the SAE involves a subject death, and is determined to be possibly, probably or definitely related to the investigational drug or any research related procedure, the event must be reported to the DSMC Chair (or Vice Chair) and DSMC Director within one business day.

1.3 Review of Adverse Event Rates

If an increase in the frequency of Grade 3 or 4 adverse events (above the rate reported in the Investigator Brochure or package insert) is noted in the study, the Principal Investigator will notify the DSMC via report at the time the increased rate is identified. The report will indicate if the incidence of adverse events observed in the study is above the range stated in the Investigator Brochure or package insert.

If at any time the Investigator voluntarily holds enrollment or stops the study due to safety issues, the DSMC Chair (or Vice Chair) and the DSMC Director must be notified within one business day and the IRB must be notified as per IRB reporting regulations.

Data and Safety Monitoring Committee Contacts:

[redacted] (DSMC Chair)
[redacted]
Box 1705
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San Francisco, CA 94158

[redacted] DSMC Director)
[redacted]
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San Francisco, CA 94143

Appendix 3 Prohibited Medications List

Drug	**Trade name (if applicable)**
BCG (Intravesical or vaccine) - ok if on ARM B	Theracys. TICE-BCG
BuPROPion	Wellbutrin
Cladribine - ok if on ARM B	Mavenclad
Conivaptan	Vaprisol
Dacomitinib	Vizimpro
Deferiprone - ok if on ARM B	Ferriprox
Dexamethasone	Prozac
Fludrocortisone	
FLUoxetine	Prozac
Hydrocortisone (topical is okay)	Cortef
Idelalisib	Zydelig
PARoxetine	Paxil
Methylprednisolone	Medrol
Ospemifene	Osphena
Prednisone	Deltisone
Tipranavir	Aptivus
Triamcinolone (topical, inhaled is ok)	Kenalog