UCSF Helen Diller Family Comprehensive Cancer Center

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Reversing Therapy Resistance with Epigenetic-Immune Modification (Pembrolizumab, Vorinostat, Tamoxifen)

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

UCSF Principal Investigator / Study Chair

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Signature Date

Abstract

Title:

Reversing therapy resistance with epigenetic-immune modification: phase II trial of Vorinostat, Tamoxifen and Pembrolizumab in hormone receptor expressing advanced breast cancer.

Patient population:

Patients with ER+ hormone therapy resistant (HRT) and ER-negative breast cancer

Rationale for study:

Background
More than two thirds of all advanced breast cancers are dependent on estrogen, and the introduction of selective estrogen receptor modulators (SERMs) has dramatically improved the survival of women with breast cancer. Unfortunately, the development of hormone therapy resistance in breast cancer is one of the most frequent causes of cancer death in women worldwide. 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 hormone therapy positive tumors, recent preclinical studies have further suggested that epigenetic priming may be even more effective in ER-negative tumors that do not respond to Immune check point inhibitors or have low PD-1/PD-L1 expression. The goal of this study is to demonstrate that Vorinostat can increase PD-1 and PD-L1 expression.

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 TNBC or ER-negative HER2-positive tumors

The role of HDAC inhibitors in breast cancer
The role of epigenetic modulation has been studied extensively in breast cancer therapy. We have previously shown that epigenetic modulation with an HDAC inhibitor can reverse hormone therapy resistance and force cells into programmed cell death[1]. Based on these preclinical studies, we had proposed two clinical trials testing HDAC inhibitors with hormonal therapy in ER+ breast cancer. In a first clinical trial, we evaluated the role of vorinostat (VOR) in reversing therapy resistance in advanced breast cancer[2]. The objective response rate by RECIST criteria was 19%, the clinical benefit rate (response or stable disease $\geq$24 weeks) was 40%, and the median response duration was 10.3 months (confidence interval: 8.1–12.4). A second trial (ENCORE 301) evaluated entinostat and exemestane. The median overall survival in the combination arm was 28.1 months compared to 19.8 months in the exemestane only arm (HR = 0.59; P = 0.036).

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[3,4]. 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[5]. 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[6].

Optimal Epigenetic Immune priming (EIP)
Based on the established role of HDAC inhibitors in reversing hormone therapy resistance to antiestrogens and aromatase inhibitors and therapy resistance in ER-negative tumors , and the provocative role of HDAC inhibitors in modulating tumor immunity, we propose to test the role of epigenetic immune priming (EIP) in acquired therapy resistance. In a three-arm Phase II trial, we will explore concurrent and sequential EIP, testing two principles:

- Sequential priming with optimal immune activation (Arm B and C) and,
- Concurrent priming with maximal dosing of both epigenetic and immune modulators (Arm A).

Primary objective:

a) To define the optimal approach for epigenetic immune priming in breast cancer on the basis of overall response rate (ORR: CR+PR+SD at 24 weeks).

b) Safety and tolerability of vorinostat, tamoxifen and pembrolizumab

Secondary objectives:

a) To define the optimal approach for epigenetic immune priming in therapy –resistant breast cancer

b) Determine the impact of vorinostat on PD-L1 expression in ER-positive tumors and ER-negative tumors

c) To assess duration of response (DOR) 24 week landmark progression free survival (PFS:24)

d) Median PFS and overall survival (OS)

e) Tumor responses will also be calculated by Immune Related Response-Criteria (irRC).

Exploratory objectives:

a) To evaluate changes in expression of immune checkpoint receptors / ligands (programmed death receptor-1 [PD-1]/programmed death ligand-1 [PD-L1]) in tumor biopsies pre- and post-therapy in tumor and immune cells.

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 in ER-positive and ER-negative tumors

Study design:

We propose a randomized two-arm trial, using Simon's 2-stage design, in ER+ patients with therapy resistant breast cancer to test the optimal sequence and dosing of epigenetic immune priming in hormone therapy resistant breast cancer. A third arm (Arm C) will include ER-negative patients who will follow the concurrent priming, but exclude tamoxifen.

The two arms all include vorinostat, TAM and pembrolizumab to evaluate

- Sequential priming – begin pembrolizumab in Cycle 1 (**Arm B and Arm C**) and,
- Concurrent priming with maximal dosing of both epigenetic and immune modulators– begin pembrolizumab on day 1 in Cycle 2 (**Arm A**)

Drug combination: We propose an exploratory biomarker study to test the combination of pembrolizumab and vorinostat.

Population:

We will test this combination in patients with tumors that may have unknown or low PD-L1 expression by prior testing (e.g. prior Keynote study screen failures). Patients may have progressed on prior PD-1/PD-L1 checkpoint inhibitors. Tumor must have less than 1% ER expression (HER2 positive or negative)

Schematic of the study design

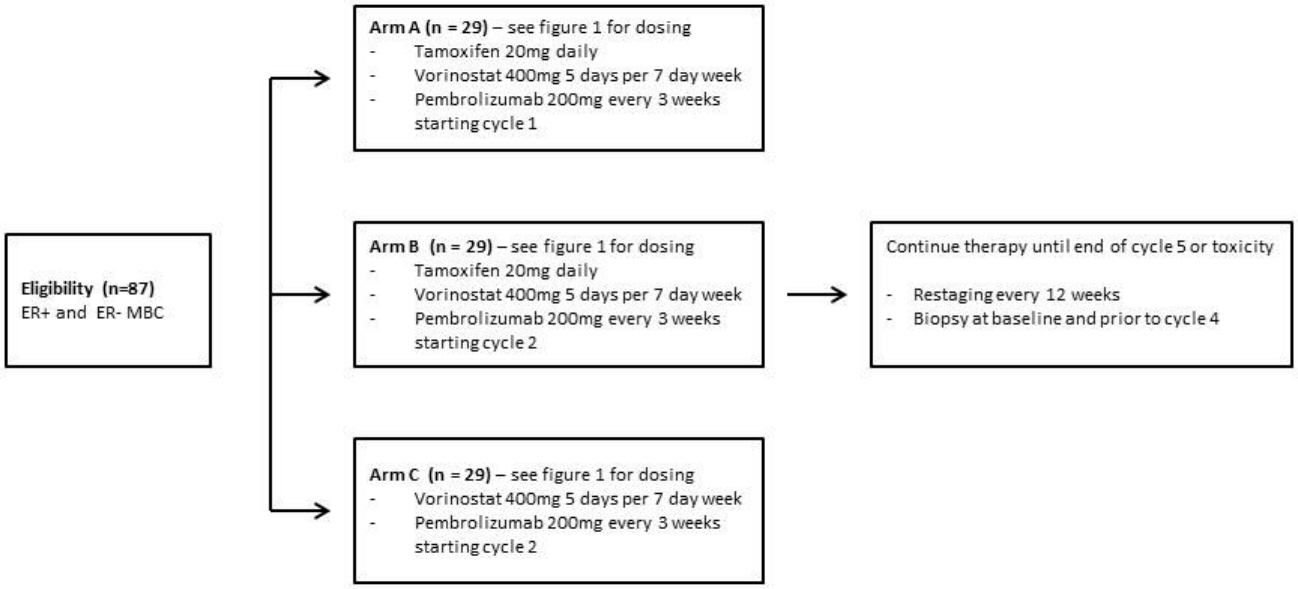
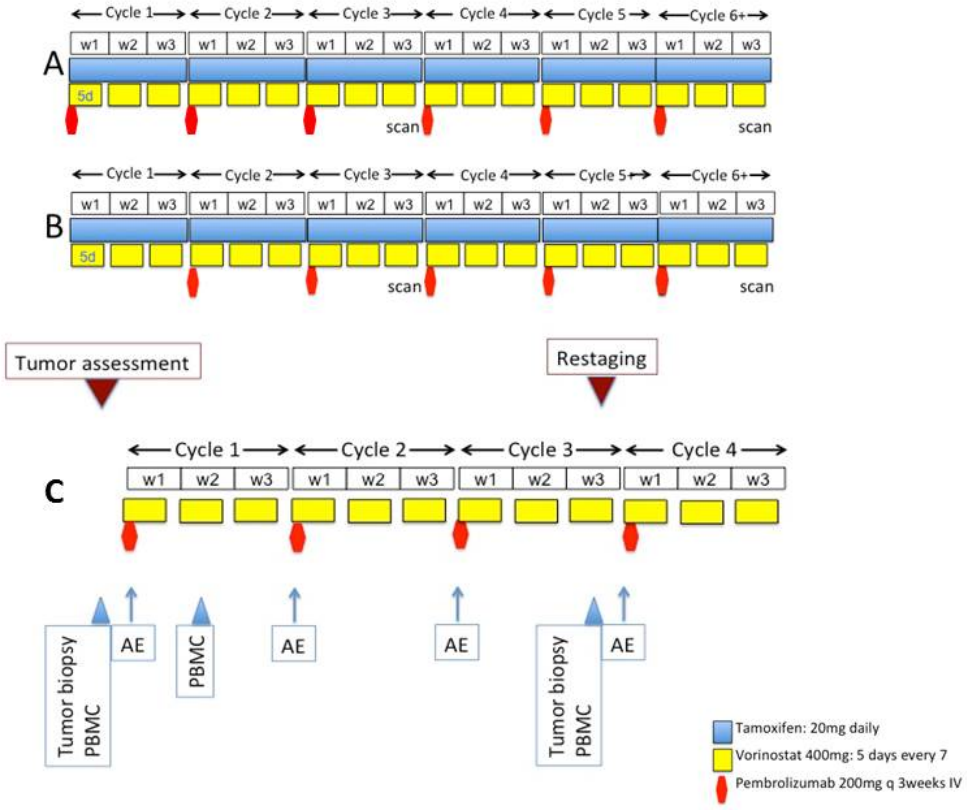


Figure 1. Schematic of dosing schedule



Number of patients:

20-87 patients

Duration of therapy:

Patients may continue treatment for 24 months from the time of study entry, and longer with permission of the sponsor and Merck.

Duration of follow up:

Patients will be followed for 30 days after completion of treatment or removal from study, and serious adverse events will be collected for 30 days after the end of treatment.

Duration of study:

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

Study drugs:

Tamoxifen (generic) is a non-steroidal selective estrogen receptor modulator (SERM) currently used in 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 extensively metabolized after oral administration, with N-desmethyl tamoxifen the major metabolite found in patients' plasma.

Vorinostat (Suberoylanilide hydroxamic acid, SAHA; Merck) is a small molecule inhibitor of histone deacetylases (HDACs) that binds directly in the enzyme's active site in the presence of a zinc ion. It targets most human Class 1 (related to the yeast transcriptional regulator Rpd3) and Class 2 (similar to the yeast Hda1) enzymes. It causes G1 or G2 phase cell-cycle arrest, apoptosis or differentiation in cultured transformed cells. Vorinostat is the most potent HDAC inhibitor that can be administered orally with excellent bioavailability.

Pembrolizumab (Merck) is a potent and highly selective humanized monoclonal antibody 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. Pembrolizumab is currently under clinical investigation.

Safety assessments:

Safety will be assessed by reviewing adverse events (AEs), laboratory evaluations, physical examination, and spontaneous reports. Each patient will be assessed periodically for the development of any toxicity according to the MCI CTCAE v4.0. All AEs and serious AEs (SAEs) will be documented and reported. We will also pay particular attention to pembrolizumab adverse events of clinical interest, which will predominantly be of immune origin.

Efficacy assessments:

For the primary endpoint, patients will be assessed for objective responses by RECIST criteria 1.1. Secondary endpoints include immune response, progression free survival, and overall survival. Monitoring of secondary endpoints will be performed via serial imaging and follow up for survival. Correlative endpoints include epigenetic modulation and immune modulation as well as their interaction.

Unique aspects of this study:

This is the first study to look at the response of hormone therapy resistant breast cancer to epigenetic immune priming. It is also the first study to look at 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.

Recent preclinical studies have further suggested that epigenetic priming may be even more effective in ER-negative tumors that do not respond to Immune check point inhibitors or have low PD-1/PD-L1 expression. The goal of this study is to demonstrate that Vorinostat can increase PD-1 and PD-L1 expression.

In a third arm the study will evaluated the role of epigenetic priming in tumors that are ER-negative.

List of Abbreviations

AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical (Classification System)
AUC	area under the curve
BUN	blood urea nitrogen
CBC	complete blood cell (count)
CHR	Committee on Human Research (UCSF IRB)
CR	complete response
CRC	Clinical Research Coordinator
CRF	case report form
CSF	cerebral spinal fluid
CT	computerized tomography
CTCEA	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
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
ECOG	Eastern Cooperative Oncology Group
ECI	event of clinical interest
FCBP	female of childbearing potential
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HBeAg	Hepatitis B “e” antigen
HBV	hepatitis B virus
HCT	hematocrit
HCV	hepatitis C virus
HDFCCC	Helen Diller Family Comprehensive Cancer Center
HGB	hemoglobin
HIV	human immunodeficiency virus
ICH	International Conference on Harmonization
IND	investigational new drug application
IP	investigational product
IRB	Institutional Review Board

List of Abbreviations

iwCLL	International Workshop on Chronic Lymphocytic Leukemia
IV	intravenous
LDH	lactate dehydrogenase
LFT	liver function test
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCI	National Cancer Institute
NHL	non-Hodgkin's lymphoma
ORR	overall response rate
PD	disease progression
PD-1	Programmed cell death 1
PK	pharmacokinetics
PO	Per os (by mouth, orally)
PR	partial response
PRC	Protocol Review Committee (UCSF)
QOL	Quality of Life
RBC	red blood cell (count)
SD	stable disease
SD	standard deviation
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
TIL	Tumor-infiltrating lymphocytes
ULN	upper limit of normal
WBC	white blood cell (count)

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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[7]. 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[8]. 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[9]. 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 postmenopausal. 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%[10,11,12,13]. The response rate to second line hormonal therapy is considerably less (10-20%)[10], suggesting a clear need for more effective therapy.[14,15,16]

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[17]. 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.

1.1.4 Immune surveillance and the role of the PD-1 pathway

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades[18]. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in

various malignancies[19,20,21,22]. 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 PDL2)[23,24]. The structure of murine PD-1 has been resolved[25]. PD-1 and its 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, PD1 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[14,15,16,23]. The mechanism by which PD-1 down modulates T-cell responses is similar to, but distinct from that of CTLA-4 as both molecules regulate an overlapping set of signaling proteins[26,27]. 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[28,29]. Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells, as well as subsets of macrophages and dendritic cells[30]. 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[26,31,32,33]. 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[26]. 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)[34]. This suggests that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and should be considered an attractive target for therapeutic intervention.

1.1.5 PD-1 and PD-L1 in breast cancer

Inhibition of the PD-L1/PD-1 axis has been a major milestone in many cancer types. However, its relevance in breast cancer remains less clear. Expression and upregulation of PD-L1 is variable in breast cancer, and found to be high in TN and HER2+ disease. Increased PD-L1 expression has been observed in hormone therapy resistance, frequently reported with loss of the progesterone receptor (PR), a measure of hormone therapy resistance[5]. Hence, PD-1 inhibitors may have a role in hormone therapy resistant breast cancer. However, PD-1 inhibitors may be more effective after epigenetic immune priming. This proposal is focused on the potential role of epigenetic immune priming to reverse hormone therapy resistance (HTR) in pre and postmenopausal breast cancer.

Recent data suggests that PD-L1 expression is low in a majority of patients, which may confer poor response to PD-1 or PD-L1 check point inhibitors. Preclinical in vitro and in vivo studies, including ours, suggests that HDAC inhibition using vorinostat increases PD-L1 transcription

and cellular expression in breast cancer cells, including ER+ hormone sensitive and resistant as well as TN cells.

1.2 Background on the Compounds

1.2.1 Tamoxifen

Tamoxifen is the most commonly used anti-estrogen or 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%)[13]. The observation of endometrial cancer (<0.5%) has been predominantly observed when used in the preventive or adjuvant setting[35]. 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.

1.2.2 Histone Deacetylases (HDAC) and their inhibitors

A promising new class of drugs showing activity in cancer is the histone deacetylase inhibitors (HDACi)[36,37]. 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[38,39]. The addition of acetyl groups to lysine residues on the N-terminal tail of histones by histone acetyl transferases (HAT) results in the weakening of the bond between histones and DNA[39]. In contrast, removal of acetyl groups by HDACs results in the condensation of the nucleosomes and has been correlated with gene silencing[39]. HDACs can be divided into at least three different classes, I-III. Each class contains several members of structurally and functionally variable HDACs[40,41]. Alterations in the regulatory function of HATs and HDACs have been associated with the development of certain cancers[42]. For example, mutations in the HAT gene CBP have been correlated with the development of certain colorectal and gastric cancers[43], whereas altered HDAC function has been associated with the onset of acute promyelocytic leukemia (APL)[42]. There are several inhibitors of HDACs that show anti-cancer activity in vitro and in vivo[44]. 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.

1.2.3 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[45]. 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[46,47]. 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[48]. 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[37,49]. The third class of HDACs (homologues 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[50]. 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)[51-55]. 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[56-61].

The antitumor activity of vorinostat was demonstrated in several in vivo models of cancer, including a xenograft model of human CWR22 prostate cancer cells[57], a mouse model of APL containing the promyelocytic leukemia zinc-finger-retinoic acid receptor α fusion gene (PLZF-RARα)[62], and an N-methylnitrosourea-induced mammary tumor model in rodents[63]. Vorinostat has also showed 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.

1.2.4 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.

1.2.4.1 Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades [1]. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies [2; 3; 4; 5; 6]. 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) [7; 8]. The structure of murine PD-1 has been resolved [9]. PD-1 and family members are type I transmembrane glycoproteins containing an Ig Variable-type (V-type) domain responsible for ligand binding and a cytoplasmic tail which is responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM). Following T-cell stimulation, PD 1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3ζ,

PKCθ and ZAP70 which are involved in the CD3 T-cell signaling cascade [7; 10; 11; 12]. The mechanism by which PD-1 down modulates T-cell responses is similar to, but distinct from that of CTLA-4 as both molecules regulate an overlapping set of signaling proteins [13; 14]. PD-1 was shown to be expressed on activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B-cells, T regs and Natural Killer cells [15; 16]. Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells [17]. The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types, including non-hematopoietic tissues as well as in various tumors [13; 18; 19; 20]. Both ligands are type I transmembrane receptors containing both IgV- and IgC-like domains in the extracellular region and contain short cytoplasmic regions with no known signaling motifs. Binding of either PD-1 ligand to PD-1 inhibits T-cell activation triggered through the T-cell receptor. PD-L1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments. PD-L2 is thought to control immune T-cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T-cell function in peripheral tissues [13]. Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor. PD-1 has been suggested to regulate tumor-specific T-cell expansion in subjects with melanoma (MEL)[21]. This suggests that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and should be considered as an attractive target for therapeutic intervention.

MK-3475 (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 without ADCC or CDC activity.

1.2.4.2 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 mono-therapy 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-□, granzyme B, and perforin, indicating that the mechanism of action involved local infiltration and activation of effector T-cell function in vivo [22; 23; 24; 25; 26; 27]. Experiments have confirmed the in vivo efficacy of PD-1 blockade as a mono-therapy as well as in combination with chemotherapy in syngeneic mouse tumor models (see the Investigator's Brochure [IB]).

1.2.4.3 Pre-clinical and Clinical Trials

Ongoing clinical trials are being conducted in advanced melanoma, non-small cell lung cancer, head and neck cancer, urothelial tract cancer, triple negative breast cancer, gastric cancer, and hematologic malignancies. For trial details please refer to the Investigator's Brochure.

Pembrolizumab has been approved in melanoma and lung cancer.

1.3 Rationale for the Proposed Study

1.3.1 Rationale for Epigenetic Immune Priming (EIP):

Clinically, epigenetic immune regulation has been implicated in priming lung cancer cells to PD-1 inhibitors which resulted in prolonged responses[3,4]. The efficacy of PD-1 inhibitors has not been established; however the expression of PD-L1 in ER+ breast cancer is low. PD-L1

expression however has been shown to be a poor predictor of survival and PD-L1 expression has been suggested to increase as ER+ tumors become resistant to therapy.

The role of epigenetic modulation has been studied extensively in breast cancer therapy. Several investigators have shown that HDAC inhibitors have immune modulatory functions, including modulation of Tregs, FoxP3 expression, changes in TIL expression, induction of PD-L1 expression and blockage of PD-1. We have previously shown that epigenetic modulation with an HDAC inhibitor can reverse hormone therapy resistance and force cells into programmed cell death[1]. Based on these preclinical studies, we had proposed two clinical trials testing HDAC inhibitors with hormonal therapy in ER+ breast cancer.

We hypothesize that pre-exposure of breast cancer cells to the HDAC inhibitor vorinostat (i.e., Arm A, sequential treatment) will result in down regulation of T-regulatory cells (Tregs) and FoxP3, which will increase the efficacy of PD-1 inhibitors, as measured by ORR, and prime cells to increased immune response. We therefore anticipate the schedule of administration may play an important role in the administration of this combination strategy.

Recent preclinical studies have further suggested that epigenetic priming may be even more effective in ER-negative tumors that do not respond to Immune check point inhibitors or have low PD-1/PD-L1 expression. The goal of this study is to demonstrate that Vorinostat can increase PD-1 and PD-L1 expression.

1.3.1.1 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[2]. 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.

1.3.1.2 Prior studies with other HDAC inhibitors in breast cancer:

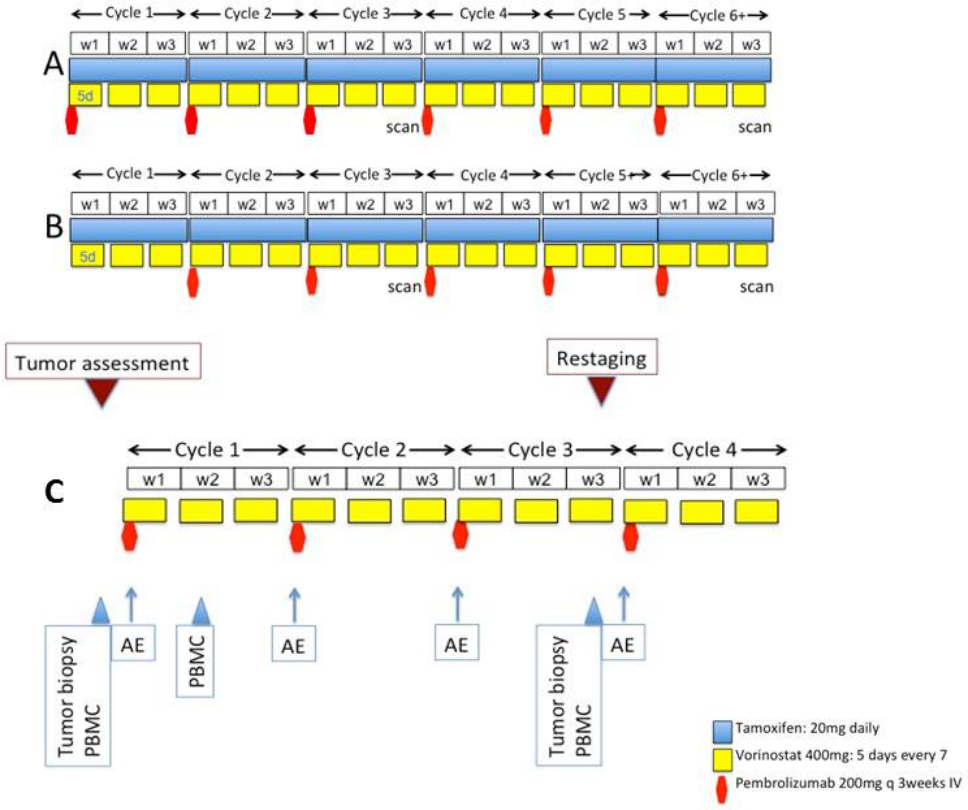
A second phase II (ENCORE 301) trial evaluated entinostat and exemestane, and treated patients with advanced estrogen receptor (ER)-positive breast cancer[66]. This study recently received Breakthrough Therapy designation from the FDA for its potential to reverse resistance to hormonal therapies. The 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). While these two studies cannot be compared directly, the preclinical studies and the clinical studies, as well as the current landscape of standard of care, will make the combination with tamoxifen more likely effective. The combination with tamoxifen will also allow enrollment of premenopausal women.

Hence the combination of HDAC inhibitors and PD-1 inhibitors may further result in an enhancement of anti-tumor efficacy of PD-1 inhibitors[6,67]. Based on the established role of HDAC inhibitors in reversing hormone therapy resistance to antiestrogens and aromatase

inhibitors and the provocative role of HDAC inhibitors in modulating tumor immunity, we propose to test the role of epigenetic immune priming (EIP) in acquired hormone therapy resistance.

In a two arm Phase II trial, we will explore concurrent and sequential EIP testing two principles: Sequential priming with optimal immune activation (Arm A) and concurrent priming with maximal dosing of both epigenetic and immune modulators (Arm B).

Figure 1. Schematic of dosing schedule



2 Objectives of the Study

2.1 Primary objective:

a) To define the optimal approach for epigenetic immune priming in hormone refractory breast cancer on the basis of overall response rate (ORR: CR+PR+SD at 24 weeks).

b) Safety and tolerability of vorinostat, tamoxifen and pembrolizumab

2.2 Secondary objectives:

a) To define the optimal approach for epigenetic immune priming in hormone –resistant breast cancer and ER-negative tumors

b) To assess duration of response (DOR) 24 week landmark progression free survival (PFS:24)

c) Median PFS and overall survival (OS)

d) Tumor responses will also be calculated by Immune Related Response-Criteria (irRC).

e) To test the response of tumor PD-L1 expression to epigenetic modulation

2.3 Exploratory objectives:

a) To assess for post-treatment changes in tumor-infiltrating lymphocyte (TIL) populations, PD-L1 expression and potential indicators of response. If tumor samples demonstrate that epigenetic therapy converts tumors from a low (baseline) to high TIL (post-treatment) but without a corresponding increase in ORR, then we can confidently reject our hypothesis that enhancing TILs will increase pembrolizumab efficacy in this tumor type.

b) Acetylation of histones in PBMCs as a pharmacodynamics response marker for vorinostat.

2.4 Endpoints

Two arm study to determine the role of sequential versus epigenetic priming of ER+ breast cancer cells.

A comparator arm in ER-negative tumors with biomarker endpoints

2.4.1 Primary Endpoints

a) Overall response rate (CR+PR and SD at 24 weeks)

b) Toxicity

2.4.2 Secondary Endpoints

a) Duration of response rate

b) 24 week landmark progression free survival (PFS:24),

c) Median PFS and overall survival (OS),

d) Tumor responses will also be calculated by Immune Related Response-Criteria (irRC)

e) To test the response of PD-L1 expression to epigenetic modulation

2.5 Exploratory Endpoints

- To assess for post-treatment changes in TIL population, PD-L1 expression and potential indicators of response. If tumor samples demonstrate that the combination therapy converts tumors from a low (baseline) to high TIL (post-treatment) but without a corresponding increase in ORR, then we can confidently reject our hypothesis that enhancing TILs will increase pembrolizumab efficacy. Acetylation of histones in PBMCs as a response marker for vorinostat.

3 Study Design

3.1 Characteristics

We propose a three arm, 20-87 patient trial in patients with hormone therapy resistant breast cancer to test the optimal sequence and dosing of epigenetic immune priming in hormone therapy resistant breast cancer. The two arms all include vorinostat, TAM and pembrolizumab to evaluate either sequential priming (Arm A) or, concurrent priming with maximal dosing of both epigenetic and immune modulators in ER+ (Arm B) and ER- (Arm C?) disease. Stage 1 of the trial will evaluate 20 patients, 10 in each arm and randomly assigned. If the response rates are adequate, the trial will proceed to Stage 2 in order to evaluate 58 patients, 29 in each arm.
Given the absence of responses in PD-L1 low patients to pembrolizumab, we will determine the benefits for vorinostat in reversing therapy resistance to pembrolizumab in ER-negative breast cancers (HER2-positive or negative)

Patients will be evaluated for response at 12 weeks 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 clinical 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 as an agent and are familiar with managing drug toxicities. In addition, we are experienced with immune-related toxicities as well.

Tissue biopsies of all patients will be collected prior to enrollment to assess for pre-treatment TIL and PD-L-1 expression. A limited number of patients with disease unamenable to biopsy will be allowed to enroll in the trial with prior approval from study PI. Follow up biopsies and peripheral blood collection will be taken from all patients post-treatment, prior to starting cycle 4, to characterize changes in local tissue effects and antigen-specific cellular and humoral immune responses in peripheral blood.

3.2 Number of Subjects

20-87 patients

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 onto 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

   ER-positive tumors

   a. Progressed after at least one line of hormonal therapy

b. Any number of prior chemotherapy in the metastatic setting
c. Any number of prior hormonal therapies.
d. HER2 positive or negative

ER-negative tumors

e. PD-L1 low, high or unknown
f. Progression after prior PD-1 or PD-L1 inhibitors allowed
g. HER2 positive or negative

2. 18 years or older.
3. Eastern Cooperative Oncology Group (ECOG) Performance Status of ≤ 2.
4. Understand and voluntarily sign an informed consent prior to any study-related assessments or procedures are conducted and are able adhere to the study visit schedule and other protocol requirements.
5. Consent to paired tumor biopsy, for accessible tumors
6. Measureable tumor by RECIST criteria v.1.1
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 within 14 days of study start:
   - 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 child-bearing potential (defined as a 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 7 days 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. Male subjects with female partner of childbearing potential must agree to the use of a physician-approved contraceptive method throughout the course of the study

3.3.2 Exclusion Criteria

1. Any significant medical condition, laboratory abnormalities, which places the subject at unacceptable risk if he/she were to participate in the study.
2. Has had prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to a previously administered agent.

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

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

    c. Patients may continue on ovarian suppression

3. Has a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or in situ cervical cancer that has undergone potentially curative therapy.
4. Any condition that confounds the ability to interpret data from the study.
5. Symptomatic central nervous system metastases. Subjects with brain metastases that have been previously treated with WBXRT and are stable for 6 weeks are allowed. Gamma or cyber knife treated lesions may enroll 2 weeks after completion if toxicities are resolved and no longer requiring steroids, patients with asymptomatic brain metastases are allowed after discussion with the study sponsor.)
6. Persistent diarrhea or malabsorption ≥ NCI CTCAE grade 2, despite medical management.
7. Unstable angina, significant cardiac arrhythmia, or New York Heart Association (NYHA) class 3 or 4 congestive heart failure.
8. Prior systemic cancer-directed treatments or investigational modalities ≤ 5 half-lives or 3 weeks, whichever is shorter, prior to starting study drug or who have not recovered from side effects of such therapy (except alopecia).
9. Has an active auto-immune disease requiring systemic treatment within the past 3 months or a documented history of clinical autoimmune disease in the past, or a syndrome that requires systemic steroids or immunosuppressive agents. Subjects with vitiligo or resolved childhood asthma/atopia would be an exception to this rule. Subjects that require intermittent use of bronchodilators or local steroid injections would not be excluded from the study. Subjects with hypothyroidism stable on hormone replacement or Sjorgen's syndrome will not be excluded from the study.
10. Has evidence of interstitial lung disease or active, non-infectious pneumonitis.
11. Has an active infection requiring systemic therapy.
12. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.
13. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.

14. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the pre-screening or screening visit through 120 days after the last dose of trial treatment. Pregnant women are excluded from this study because vorinostat, tamoxifen and PD-1 are drug classes with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother, breastfeeding should be discontinued if the mother is treated with vorinostat, tamoxifen and PD-1 inhibitors.
15. Active and ongoing steroid use, except for non-systemically absorbed treatments (such as inhaled or topical steroid therapy for asthma, COPD, allergic rhinitis).
16. Major surgery ≤ 2 weeks prior to starting a study drug or who have not recovered from side effects of such therapy.
17. Known hypersensitivity to pembrolizumab or any of its insipients.
18. Has received a live vaccine within 30 days prior to the first dose of trial treatment.

3.4 Duration of Therapy

In the absence of treatment delays due to adverse events, treatment may continue for 24 months or until:

- Clearly documented disease progression
- Inter-current illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Patients decides to withdraw from the study
- Significant patient non-compliance with protocol
- General or specific changes in the patients' condition render the patient unacceptable for further treatment in the judgment of the investigator.
- Patients may receive palliative radiation therapy for isolated symptomatic lesions

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 7.4

· 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

3.5 Duration of Follow Up

Patients will be followed for 30 days after completion of treatment 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 6.2.7

3.6 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.

No randomization is required for ER-negative patients (patients must have biopsiable disease)

3.7 Study Timeline

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 5.1). Trial treatment may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons. All trial treatments will be administered on an outpatient basis. pembrolizumab will be administered as a 30 minute IV infusion (treatment cycle intervals may be increased due to toxicity as described in Section 5.2.1.2). Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min)

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3.7.1 Clinical Criteria for Early Trial Termination

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

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

4. Plans to modify or discontinue the development of the study drug

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

4 Study Drugs

4.1 Description, Supply and Storage of Investigational Drugs

4.1.1 Investigational Drug Tamoxifen

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.

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.

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.

How Supplied:
Tamoxifen (generic) is commercially available. (AstraZeneca has discontinued the commercial manufacture and distribution of branded NOLVADEX® tablets in the United States as of June 2006)

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

Complete and updated adverse event information is available in the Investigational Drug Brochure and product package insert.

4.1.2 Investigational Drug Vorinostat (Zolinza, NSC 701852)

Vorinostat is available in size 3 capsules containing 100 mg of Vorinostat for administration.

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

Storage:
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.

Method of Administration:
Unless otherwise stated in the protocol, vorinostat capsules must be administered whole. Administer doses of vorinostat with food, if possible.

Potential Drug Interactions:
The major pathways of vorinostat metabolism involve glucuronidation and β-oxidation. As vorinostat is not eliminated via CYP450 pathways, no drug-drug interactions are expected with known CYP450 inhibitors or inducers. Although vorinostat was not a potent reversible CYP450 inhibitor, studies performed to monitor gene expression changes indicated some potential for CYP2C9 and CYP3A4 activity suppression. However, these changes were observed at concentrations higher than the pharmacologically relevant concentration of 2 μM (Cmax).
Prothrombin time and INR prolongations have been reported in patients taking vorinostat concomitantly with coumarin derivative anticoagulants. Monitor these patients more frequently for alterations in their coagulation parameters.

Special Handling:
Vorinostat is an anticancer drug. If clean powder is spilt 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.

Patient Care Implications:
Because vorinostat's dose limiting toxicities are anorexia, dehydration, diarrhea, and fatigue, patients should maintain adequate fluid and food intake. Encourage patients to seek a nutritional consult. 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. Daily dose should not exceed 16 mg/day. Loperamide should not be taken prophylactically. Advise patients to drink plenty of clear fluids to help prevent dehydration caused by diarrhea. Avoid loperamide if there is the presence of blood or mucus in the stool or if diarrhea is accompanied by fever. If grade 3 or 4 diarrhea develops, discontinue further treatment with vorinostat. Patients should not have taken valproic acid, another histone deacetylase inhibitor, for at least 2 weeks prior to study enrollment.

How Supplied:
Vorinostat is supplied by Merck & Co., Inc. Vorinostat will be provided in a 100-120 tablet bottle. For the purpose of this study, vorinostat will be given at 400 mg per day (4x 100 mg tablets), 5 of 7 days. Please refer to complete prescribing information in the FDA packet insert for storage and handling.

4.1.3 Investigational Drug MK-3475 (Pembrolizumab)

Pembrolizumab will be available in 100mg solution in a single use-vial for intravenous administration.

Classification
Antineoplastic

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.

Contraindications
None

Availability
Pembrolizumab is an investigational agent supplied by Merck, for storage and application please refer to lab manual.

Summary
The programmed cell death 1 (PD-1) pathway represents a major immune control switch which may be engaged by tumor cells to overcome active T-cell immune surveillance.
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. This blockade enhances functional activity of the target lymphocytes to facilitate tumor regression and ultimately immune rejection.

Merck is studying pembrolizumab for various oncology indications. An open-label Phase I study is being conducted to evaluate the safety and clinical activity of pembrolizumab when administered as monotherapy. The dose escalation portion of this study evaluated three dose levels of single agent pembrolizumab (1 mg/kg, 3 mg/kg, and 10 mg/kg), in patients with advanced solid tumors. All three dose levels were well tolerated and no dose-limiting toxicities (DLTs) were observed, therefore the maximum tolerated dose (MTD) has not been determined. The ongoing expansion part of this study is evaluating pembrolizumab in patients with melanoma (MEL) and non-small cell lung cancer (NSCLC).

In a Phase II study, is also being conducted to evaluate the safety and clinical activity of pembrolizumab relative to standard of care chemotherapy in melanoma.

In a randomized, controlled, open-label, three-arm Phase III pivotal study is being conducted to evaluate two dosing regimens of pembrolizumab versus ipilimumab (IPI) in patients with unresectable or metastatic MEL who have not received IPI treatment. Protocol 010 (PN010), a randomized, adaptively designed Phase II/III trial is being conducted to evaluate two dosing schedules of pembrolizumab (10 mg/kg Q3W or 2 mg/kg Q3W) versus docetaxel in patients with NSCLC with PD-L1 positive tumors who have experienced disease progression after platinum-containing systemic therapy.

In an open-label, non-randomized, Phase I study is evaluating pembrolizumab alone in Japanese patients with advanced solid tumors and in combination with cisplatin/pemetrexed and carboplatin/paclitaxel in patients with advanced NSCLC. The combination therapy portion of the trial had not yet initiated as of 18-Oct-2013.

In a nonrandomized, multi-cohort trial is evaluating pembrolizumab 10 mg/kg Q2W in patients with PD-L1 positive advanced solid tumors. Cohort A is enrolling patients with triple negative breast cancer, Cohort B is enrolling patients with squamous cell carcinoma of the head and neck, Cohort C is enrolling patients with urothelial tract cancer of the renal pelvis, ureter, bladder, or urethra. As of the cut-off date of 18-Oct-2013, Cohort D which will enroll patients with adenocarcinoma of the stomach or gastroesophageal junction had not yet initiated. Safety data are continuing to accumulate in the clinical development program across multiple indications; immune-related adverse events (irAEs) are expected based on the nature of the compound, its mechanism of action and reported experience with immunotherapies that have a similar mechanism of action.

Nonclinical Pharmacology

Pembrolizumab strongly enhances T-lymphocyte immune responses in cultured blood cells from healthy human donors, cancer patients, and primates. In T-cell activation assays using human donor blood cells, the EC50 (concentration where 50% of the maximum effect is achieved) has been ~0.1 to 0.3 nM. In addition to interleukin-2 (IL-2), tumor necrosis factor alpha (TNFα), interferon gamma (IFNΩ), and levels of other cytokines were modulated by pembrolizumab. The antibody potentiates existing immune responses only in the presence of antigen and does not nonspecifically activate T-cells.

Using an anti-murine PD-1 analog antibody, PD-1 blockade has been shown to significantly inhibit tumor growth in a variety of syngeneic murine tumor models. In these experiments in mice, anti-PD-1 therapy is synergistic with chemotherapeutic agents such as gemcitabine and 5-fluorouracil (5-FU) and combination therapy results in increased complete tumor regression rates in vivo.

Nonclinical Pharmacokinetics

After intravenous (IV) administration of pembrolizumab to cynomolgus monkeys, systemic exposure to pembrolizumab independent of sex, increased with increasing dose. Systemic exposure for the 7-day dosing interval increased after repeated dosing from 40 to 200 mg/kg. Area under the concentration-time curve (AUC) for the 7-day dosing interval (AUC[0-7 days]) after one dose appeared to be dose-proportional from 0.3 to 200 mg/kg, suggesting dose-independent pharmacokinetics (PK). Terminal half-life (t½) values from individual animals after repeated IV dosing ranged from 11.8 to 23.7 days (mean values ranged from 15.7 to 22.3 days) across the doses tested.

Safety Pharmacology/Toxicology

The potential for systemic toxicity of pembrolizumab was assessed in a 1-month repeat-dose toxicity study with a 4-month recovery in cynomolgus monkeys and in a 6-month repeat dose toxicity study with a 4-month recovery period in cynomolgus monkeys. In the 1- month toxicity study, cynomolgus monkeys were administered an IV dose of 6, 40, or 200 mg/kg once weekly for a total of five doses. Four monkeys/sex/group were euthanized during Week 5. The remaining two monkeys/sex/group were euthanized during Week 23, after a four-month post-dose period. In this study, pembrolizumab was well tolerated in monkeys with the systemic exposure (AUC) up to approximately 170,000 µg/ day/mL over the course of the study. There was no test article-related mortality, and test article-related changes were limited to an increased incidence of inguinal swelling, and increased splenic weights in males receiving 200 mg/kg. Both of these findings were not considered adverse and there was no histopathologic correlation. Splenic weights were normal at the post-dose necropsy. Anti-pembrolizumab antibodies were detected in seven (out of eight) animals in the 6 mg/kg dose group and one (out of eight) animal in the 40 mg/kg dose group, and were associated with an apparent increase in clearance of pembrolizumab. The presence of anti-drug antibodies (ADA) in monkeys in the low-dose group and in one monkey in the mid-dose group did not impact the pharmacodynamic response as sufficient target engagement was demonstrated for the duration of the study (with the exception of one low-dose monkey). Additionally, anti-pembrolizumab antibodies were not detected in any monkeys in the high-dose group, suggesting that potential toxicity has been evaluated at the highest exposure levels in the study. Based on the lack of adverse test article-related findings in this study, the No Observable Adverse Effect Level (NOAEL) was ≥200 mg/kg.

In the 6-month toxicity study, the potential for systemic toxicity was assessed in cynomolgus monkeys administered an IV dose of 6, 40, or 200 mg/kg once every other week for approximately 6 months (a total of 12 doses) followed by a 4-month treatment free period. Three animals/sex/group were designated for interim necropsy at the end of the 6-month dosing phase (3 days after receiving the last dose in Study Week 23); and the remaining monkeys were designated for final necropsy following the 4-month treatment-free period. Pembrolizumab was well tolerated at all dose levels. There were no test article-related antemortem findings. There were no test article-related electrocardiographic or ophthalmic findings. There were no test article-related changes at injection sites. There were no test article-related gross observations or organ weight changes at the interim or final necropsy. Since there were no test article-related histomorphologic findings at interim necropsy, histomorphologic evaluation of tissues collected at final necropsy were not conducted. The presence of ADA was observed in five out of ten animals at 6 mg/kg/dose during the dosing phase, which correlated with an apparent increased rate of elimination of pembrolizumab in these animals. No anti-pembrolizumab antibodies were detected at 40 or 200 mg/kg/dose during the dosing phase, and no MK-3475 serum concentration profiles in these two groups suggested an effect of ADA on pembrolizumab elimination rate. During the treatment-free period, anti-pembrolizumab antibodies were detected in two animals at 6 mg/kg/dose, which already had ADA present during the dosing phase, and in two additional animals (one at 6 mg/kg/dose and one at 200 mg/kg/dose), which were ADA negative during the dosing phase. The detection of anti-pembrolizumab antibodies had a minimal effect on the mean group systemic exposure to pembrolizumab during the study and

did not impact the evaluation of potential toxicity of MK- 3475 for the duration of the 6-month study as there were no test article-related effects on any of the parameters examined and as no monkey in the mid- and high-dose groups developed ADA during the dosing phase. In conclusion, pembrolizumab administered once every other week over a 6-month duration to cynomolgus monkeys was well tolerated and the no observed effect level (NOEL) was ≥200 mg/kg/dose (the highest dose tested). In addition, tissue cross-reactivity studies using monkey and human specimens were conducted to evaluate the potential cross reactivity of pembrolizumab with cryosections of cynomolgus monkey tissues and normal human tissues. Results demonstrated the expected on-target staining of the membranes of mononuclear leukocytes in both species. The off-target staining (cytoplasmic and stromal) that occurred in many tissues of both species was considered spurious binding inherent to the experimental conditions of the in vitro tissue cross reactivity studies with no *in vivo* toxicological significance.

Clinical Development

Clinical data from PN001 is presented in ths report with a visit cut-off date of 26-Jul-2013. As of 26-Jul-2013, there have been 789 patients treated in PN001 with pembrolizumab as a 30-minute IV infusion. Of these 789 patients, preliminary data are presented in this report from 479 patients. Data from 200 patients in Part B3 and 110 patients in Part F that were treated as of the cut-off data were not included in the analyses yet. Based upon this safety database consisting of patients treated up to 10 mg/kg once every two to three weeks, pembrolizumab has been generally well-tolerated at doses up to 10 mg/kg every other week without DLTs. One (0.002%) patient assayed to date had samples confirmed positive for ADA, but no impact on safety has been observed. Five other clinical studies (PN002, PN006, PN010, PN011, and PN012) are ongoing however preliminary data analyses are not yet available. Important safety findings from these studies will be discussed in Section 5 of this report. For these 5 studies, the number of treated patients indicated in this report is based on a visit cut-off date of 18-Oct-2013 to allow for more mature enrollment data and align with the Development Safety Update Report data cutoff date.

Pembrolizumab PK results have been obtained from PN001 following the first dose at 1, 3 and 10 mg/kg IV of pembrolizumab administered to 17 patients with solid tumors. The observed pharmacokinetic profile of pembrolizumab was typical of other IgG mAbs with a half-life (t½) of approximately 2 to 3 weeks. There was no indication of dose dependency of half-life in the 3 dose groups and a dose related increase in exposure was observed from 1 to 10 mg/kg. The long half-life supports a dosing interval of every 2 or 3 weeks. Exposure obtained with sparse sampling after dosing melanoma and non-small cell lung cancer (NSCLC) patients at 2 and 10 mg/kg, every 2 or 3 weeks, is consistent with this profile.

As of 18-Oct-2013, PN002 has randomized 497 patients with metastatic melanoma (495 patients were treated) across 3 treatment groups as follows, pembrolizumab 2 mg/kg Q3W, pembrolizumab 10 mg/kg Q3W, and chemotherapy (investigator choice of treatment) in a 1:1:1 ratio. PN006 has randomized 68 IPI-naïve patients with unresectable or metastatic melanoma across the 3 treatment groups: 10 mg/kg Q2W, 10 mg/kg Q3W, and ipilimumab in a 1:1:1 ratio. PN010 has randomized three patients with NSCLC across the 3 treatment groups: 10 mg/kg Q3W, 2 mg/kg Q3W, and docetaxel 75 mg/m2 Q3W in a 1:1:1 ratio. In PN011 10 patients have been treated. In PN012, 109 patients have been treated across the three cohorts as of 18-Oct-2013.

4.2 Drug Accountability

The Investigational Pharmacist will manage drug accountability records.

4.3 Drug Ordering

UCSF will obtain pembrolizumab (MK-3475) directly from Merck as study supply.

4.4 Packaging and Labeling of Study Drugs

Drugs will be packaged and labeled per UCSF institutional standards, adhering to applicable local and federal laws.

5 Treatment Plan

5.1 Dosage and Administration

The dose regimen of 200 mg Q3W of pembrolizumab is planned for all urothelial cancer trials. Available PK results in subjects with melanoma, NSCLC, and other solid tumor types support a lack of meaningful difference in PK exposures obtained at a given dose among tumor types. An open-label Phase 1 trial (PN001) in melanoma subjects is being conducted to evaluate the safety and clinical activity of single agent pembrolizumab. The dose escalation portion of this trial evaluated three dose levels, 1 mg/kg, 3 mg/kg, and 10 mg/kg, administered every 2 weeks (Q2W) in subjects with advanced solid tumors. All three dose levels were well tolerated and no dose-limiting toxicities were observed. This first in human study of pembrolizumab showed evidence of target engagement and objective evidence of tumor size reduction at all dose levels (1 mg/kg, 3 mg/kg and 10 mg/kg Q2W). No maximum tolerated dose (MTD) has been identified.

In KEYNOTE-001, two randomized cohort evaluations of melanoma subjects receiving pembrolizumab at a dose of 2 mg/kg versus 10 mg/kg Q3W have been completed. The clinical efficacy and safety data demonstrate a lack of clinically important differences in efficacy response or safety profile at these doses. For example, in Cohort B2, advanced melanoma subjects who had received prior ipilimumab therapy were randomized to receive pembrolizumab at 2 mg/kg versus 10 mg/kg Q3W. The overall response rate (ORR) was 26% (21/81) in the 2mg/kg group and 26% (25/79) in the 10 mg/kg group (full analysis set (FAS)). The proportion of subjects with drug-related adverse events (AEs), grade 3-5 drug-related AEs, serious drug-related AEs, death or discontinuation due to an AE was comparable between groups or lower in the 10 mg/kg group.

Available pharmacokinetic results in subjects with melanoma, NSCLC, and other solid tumor types support a lack of meaningful difference in pharmacokinetic exposures obtained at a given dose among tumor types. Population PK analysis has been performed and has confirmed the expectation that intrinsic factors do not affect exposure to pembrolizumab to a clinically meaningful extent. Taken together, these data support the use of lower doses (with similar exposure to 2 mg/kg Q3W) in all solid tumor indications. 2 mg/kg Q3W is being evaluated in NSCLC in PN001, Cohort F30 and PN010, and 200 mg Q3W is being evaluated in head and neck cancer in PN012, which are expected to provide additional data supporting the dose selection.

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 are 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.

Table 5.1 Regimen Description

Arm A (Figure 1)

Study Drug	Dose	Route	Schedule	Cycle Length
Tamoxifen	20 mg Tablets	Oral	daily continuous All cycles	3 weeks (21 days)
Vorinostat	400 mg	Oral	Days 5/7 All cycles	
Pembrolizumab	200 mg	Intravenous	Day 1, week 1 **Cycles 1+**	

Arm B (Figure 1)

Study Drug	Dose	Route	Schedule	Cycle Length
Tamoxifen	20mg Tablets	Oral	daily continuous All cycles	3 weeks (21 days)
Vorinostat	400mg	Oral	Days 5/7 All cycles	
Pembrolizumab	200mg	Intravenous	Day 1, week 1 **Cycles 2+**	

Arm C (Figure 1)

Study Drug	Dose	Route	Schedule	Cycle Length
Vorinostat	400 mg	Oral	Days 5/7 All cycles	3 weeks (21 days)
Pembrolizumab	200 mg	Intravenous	Day 1, week 1 **Cycles 1+**	

5.1.1 Dose Modifications and Dosing Delays

The following dose modification rules will be used with respect to potential toxicity. Toxicity will be assessed continuously according to the NCI Common Terminology Criteria for Adverse Events Version 4.0 (CTCAE v4.0)

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.

5.1.1.1 Dose Modifications and Dosing Delays Tables for Drug Related Adverse Events

Hematologic toxicity

Neutropenia:

Neutropenia Febrile neutropenia	Vorinostat	Tamoxifen
ANC ≥1000	100%	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	100%
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: remove from study	100%

#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.

Patients who developed a second episode of **febrile neutropenia** despite a dose modification will be removed from study.

Anemia

Hemoglobin	Vorinostat	Tamoxifen
>8 mg/dl	100 %: 400 mg qd	100%

6.5-8 mg/dl	75 %: 300 mg qd	100%
<6.5 mg/dl	50 %: 200 mg qd	100%

An alternative to dose modification would be the use of PRBC transfusion. This is not allowed in cycle one, but may be used at the discretion of the treating physician for subsequent cycles.

Thrombocytopenia

Platelets	Vorinostat	Tamoxifen
>75'000	100 %: 400 mg qd	100%
≤75'000	100 %: 400 mg qd	100%
≤50'000/mm3	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	100%
≤25'000/mm3	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	100%

Non-hematological toxicities

Laboratory abnormalities must be clinically relevant and dose and drug related to prompt dose modifications.

Bilirubin	Vorinostat	Tamoxifen
≤1.5 mg/dl	100 %: 400 mg qd	100%
1.6 – 3.0 mg/dl	75 %: 300 mg qd	100%

>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	100%
AST/ALT	Vorinostat	Tamoxifen
≤2.5 x ULN	100 %: 400 mg qd	100%
2.5-5 x ULN	First occurrence: 75 %: 300 mg qd Second occurrence: 50 %: 200 mg qd	100%
> 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	100%

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 Principle 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.

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

Fatigue	Vorinostat	Tamoxifen
Grade 1	100%	100%
Grade 2	Hold until toxicity is ≤grade 1, then resume at dose given in prior cycle.	100%
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.	100%.

Other	Vorinostat	Tamoxifen
Grade 1	100%	100%
Grade 2	Hold until toxicity is ≤grade 1, then resume at dose given in prior cycle.	100%
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.	100%
Grade 4	Discontinue protocol therapy.	100%

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.

5.1.1.2 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.

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

Table 5.1 below shows treatment guidelines for subjects who experience an infusion reaction associated with administration of pembrolizumab.

Table 5.1 Infusion Reaction Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for < =24 hrs	**Stop Infusion and monitor symptoms.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g. from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. **Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.**	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic).
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS	No subsequent dosing

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	Acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **Subject is permanently discontinued from further trial treatment administration.**	
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration. For Further information, please refer to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE) at http://ctep.cancer.gov		

5.1.1.3 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 5.12.

Table 5.12 Recommended Approach to Handling Pneumonitis

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

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

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

5.2 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 v4.0. Dose adjustments will be made according to the system showing the greatest degree of toxicity.

5.2.2 Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be reported 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 7.8.1 - Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor, that is not associated with clinical symptoms or abnormal laboratory results.

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

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

6 Study Procedures and Observations

6.1 Treatment Duration

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.

For Arm A: After the initial treatment with vorinostat and tamoxifen, regardless of response of the staging studies, PD-1 will be added to all patients.

For Arm B: patients may remain on study if there is radiological progression however the clinical presentation shows improvement or benefit.

All patients will be restaged during week 9 and 18 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.

6.2 Schedule of Procedures and Observations

The study-specific assessments are detailed in this section and outlined in Section 6 Schedule of Study Procedures and Assessments. Screening assessments must be performed within 28 days prior to the first dose of investigational product. Any results falling outside of the reference ranges may be repeated at the discretion of the investigator. All on-study visit procedures are allowed a window of ± 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.
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 patients who are consented will be registered in OnCore®, the UCSF Helen Diller Family Comprehensive Cancer Center Clinical Trial Management System (CTMS). The system is password protected and meets HIPAA requirements.

6.2.2 Long Term/Survival Follow-up Procedures

Safety Follow-Up Visit

The mandatory Safety Follow-Up Visit should be conducted approximately 30 days after the last dose of trial treatment or before the initiation of a new anti-cancer treatment, whichever comes first. All AEs that occur prior to the Safety Follow-Up Visit should be recorded. Subjects with an

AE of Grade > 1 deemed related to study drug, will be followed until the resolution of the AE to Grade 0-1, baseline or until the beginning of a new anti-neoplastic therapy.

Follow-up Visits

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

Survival Follow-up

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

6.2.3 Discontinuation of Therapy

The Investigator will withdraw a patient whenever continued participation is no longer in the patient's best interests. Reasons for withdrawing a patient include, but are not limited to, disease progression, the occurrence of an adverse event or a concurrent illness, a patient's request to end participation, or simply significant uncertainty on the part of the Investigator that continued participation is prudent. There may also be administrative reasons to terminate participation, such as concern about a patient's compliance with the prescribed treatment regimen.

When a subject discontinues/withdraws prior to trial completion, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.2 - Assessing and Recording Adverse Events. Subjects who a) attain a CR or b) complete 24 months of treatment with combination of vorinostat, tamoxifen or pembrolizumab may discontinue treatment with the option of restarting treatment if they may derive further benefit in the opinion of the study team. Tamoxifen should be continued. After discontinuing treatment following assessment of CR, these subjects should return to the site for a Follow-up Visit every 12 weeks with staging studies as described for patients on active treatment.

Table 6. Study Calendar

Test/Study	Baseline[a] screening		Cycle 1			Cycle 2	Subsequent cycles[g]	Restaging or off study
		D1	D8	D10 -12	D15	D1		
History	X	X	X		X	X	X	
Concomitant medication	X	X	X		X	X	X	
Physical Exam, Vitals & ECOG	X	X	X		X	X	X	
Height and weight	X	X	X		X	X	X	
Toxicity Assessment	X	X	X		X	X	X	X[b]
PK sample	X or D1[f]			X[h]			X[f] (end of cycle 3)	
Tumor FNA/Biopsy	X or D1[f]						X[f] (end of cycle 3)	
PBMC	X or D1[f]			X[h]			X[f] (end of cycle 3)	
Lymphocyte Subset	X or D1 [f]			X[h]			X[f] (end of cycle 3)	
CBC w/diff	X	X	X		X	X	X	
Comprehensive metabolic panel[i]	X	X	X		X	X	X[c]	
Thyroid Function	X					X	X(odd cycles)	
CEA, Ca15-3, Ca 125 (If clinically indicated)	X	X				X	X[c]	
Pregnancy Test	X[d]						X[d]	
Radiology (CT scans, MRI)	X[e]						X[e]	X[e]
Documentation of Response							X	
Vorinostat	400 mg once a day, 5 days on, 2 days off, weekly every cycle							
Tamoxifen	20 mg once a day continuously (for ER+ disease only)							
Pembrolizumab Arm A)	200 mg q every three weeks start on **day 1 of cycle 1**							
Pembrolizumab Arm B)	200 mg q every three weeks start on **day 1 of cycle 2**							

a) 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

b) 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
c) Every month for the first 6 cycles, then at least every 3 cycles thereafter, more frequently if clinically indicated
d) For women of childbearing potential, performed within 7 days of starting treatment. Pregnancy test will be repeated if clinically indicated.
e) Staging studies within 30 days prior to day of start, restaging after cycle 3 (week9), 6 (week 18), 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.
f) Pre-study within 14 days, and end of cycle 3 (preferably day 17-19) prior to cycle 4 day 1 pembrolizumab infusion.
g) Cycle delays up to 5 days for non-medical reason (e.g. holidays) are acceptable without notification of regulatory agencies.
h) On day 10-12 pre-dose.
i) Sodium, Potassium, Chloride, blood urea nitrogen, Creatinine, Non-fasting glucose, Calcium, Magnesium, Phosphorus, ALT, AST, Alkaline Phosphatase, Albumin, Total Bilirubin, Total Protein
j) 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

6.2.4 Logistics for Correlative studies

6.2.4.1 PK for vorinostat (vorinostat blood sample handling procedures)

Labeling:

1. Preprinted bar-coded PK sample labels with patient's allocation number and prescribed collection time for the collection tubes.
2. Labels should be attached to the red-top Vacutainer tube and NUNC™ tube before the blood is collected.

Procedures:

1. Label red-top Vacutainer tube (no anticoagulant) with preprinted bar-coded PK sample labels.
2. Collect 5.0 mL whole blood in the labeled red-top vacutainer tube. If blood is being collected from a central or PIC line, collect a 10 mL discard sample first before collecting the actual PK samples.
3. Invert the tube several times and allow the blood sample to clot at room temperature for 30 minutes.
4. Centrifuge the clotted sample at 2,000 x g for 15 minutes at 4°C.
5. Transfer the serum to 3.6 mL NUNC internal thread round bottom cryotubes (NUNC 366524) with the bar-coded PK sample **label** attached.
6. Samples will be stored at -70°C until processing

6.2.4.2 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 in 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.

6.2.4.3 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.

6.2.4.4 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.

Exploratory Objectives

1. To define the treatment-induced effects on circulating immune cells.
2. To assess the presence of antigen-specific immune responses to a broad panel of candidate tumor antigens.

At the prespecified endpoints: we will obtain

- Immunohistochemistry and gene expression analysis for immune cell subset quantification and localization within tumors
- Flow cytometry to evaluate changes in intra-tumoral and circulating immune cells
- T cell receptor (TCR) deep sequencing of tissue samples from pre-treatment biopsies and post-treatment biopsies, and post-treatment circulating T cells.
- Immune response mRNA expression analysis to derive signatures associated with tumor response
- Identification of genomic mutations and gene copy aberrations associated with response and resistance to therapy
- Antigen array-base detection of circulating antibody responses

These assays will be obtained in conjuction with Dr. Michael Rosenblum's lab.

6.3 Usage of Concurrent/Concomitant Medications

6.3.2 Acceptable Concomitant Medications

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

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

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 anti-diarrheals 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).

6.3.3 Prohibited Concomitant Medications

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

- 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 to 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.

6.3.4 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 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 5.6.1.1 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 7.2.2-Reporting of Pregnancy and Lactation to the regulatory agencies and to Merck. If there is any question that a subject will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

7 Reporting and Documentation of Results

7.1 Evaluation of Efficacy (or Activity)

7.1.1. Antitumor Effect

Response and progression in this study will be evaluated using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee [JNCI 92(3):205-216, 2000] as well as Immune Related Response-Criteria (irRC).]. Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST v1.1 criteria (or International Workshop on Chronic Lymphocytic Leukemia [IWCLL]).

7.1.2 Definitions

Evaluable for toxicity

All patients will be evaluable for toxicity from the time of their first treatment with the study drug.

Evaluable for objective response

Only those patients 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 patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of Cycle 1 will also be considered evaluable.)

7.1.3 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.

Target lesions

All measurable lesions up to a maximum of 5 lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and recorded and measured at baseline. Target lesions will be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor response.

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 measureable 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)

7.2.1 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.

7.2.2 Clinical Lesions:
Lesions will only be considered measurable when they are superficial (e.g., skin nodules, palpable lymph nodes). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is recommended. If measured by calipers, measurements have to be confirmed by two independent health care professionals.

7.2.3 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.

7.2.4 Conventional CT and MRI:
Imaging should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to the chest, abdomen, and pelvis.

7.3 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 SLD of target lesions, taking as reference the smallest sum SLD recorded since the treatment started and minimum 5 mm increase over the nadir, or the appearance of one or more new lesions.

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).

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 patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Table 7 Response Criteria

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Response for this Category Also Requires
CR	CR	No	CR	> 4 weeks confirmation
CR	Non-CR/ Non-PD	No	PR	> 4 weeks confirmation
PR	Non-PD	No	PR	
SD	Non-PD	No	SD	documented at least once > 4 weeks from baseline
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD*	Yes or No	PD	
Any	Any	Yes	PD	

* In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression

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.

7.4 Evaluation of Safety

Analyses will be performed for all patients having received at least one dose of study drug. The study will use the CTCAE v4.0 for reporting of non-hematologic adverse events and modified criteria for hematologic adverse events, see Section 7.5.

For multicenter studies, the Principal Investigator at the UCSF Coordinating Center will hold the role of Study Chair. The Study Chair is responsible for the overall conduct of the study and for monitoring its safety and progress at all participating sites.

7.5 Adverse Events

7.5.1 Adverse Event (AE) Monitoring

The investigator or qualified designee will assess each subject to evaluate for potential new or worsening AEs as specified in the Trial Flow Chart and more frequently if clinically indicated. Adverse experiences will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE Version 4.0 (see Section 7.5). Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

All AEs of unknown etiology associated with pembrolizumab exposure should be evaluated to determine if it is possibly an event of clinical interest (ECI) of a potentially immunologic etiology (irAE).

Please refer to section 7.5 for detailed information regarding the assessment and recording of AEs.

7.5.2 Definition of 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.

7.5.3 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.

7.5.3.1 Suspected

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.

7.5.3.2 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 patients exposed to drugs in the ACE 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.

7.5.3.3 Serious

An adverse event or suspected adverse reaction is considered serious if, in the view of either the study PI or Merck, 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 patient or subject 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.

7.5.3.4 Life-threatening

An adverse event or suspected adverse reaction is considered life-threatening if, in the view of either the study PI or Merck, its occurrence places the patient or subject 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.

7.6 Evaluation of an Adverse Event

All grade 3 and above adverse events will be entered into OnCore®, whether or not the event is believed to be associated with use of the study drug. Data about these events and their severity will be recorded using the NCI CTCAE v4.0.

The Investigator will assign attribution of the possible association of the event with use of the investigational drug, and this information will be entered into OnCore® using the classification system listed below:

Relationship	Attribution	Description
Unrelated to investigational drug/intervention	Unrelated	The AE is clearly NOT related to the intervention
	Unlikely	The AE is doubtfully related to the intervention
Related to investigational drug/intervention	Possible	The AE may be related to the intervention
	Probable	The AE is likely related to the intervention
	Definite	The AE is clearly related to the intervention

Signs or symptoms reported as adverse events will be graded and recorded by the Investigator according to the CTCAE. When specific adverse events are not listed in the CTCAE they will be graded by the Investigator as none, mild, moderate or severe according to the following grades and definitions:

Grade 0 No AE (or within normal limits)

Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated

Grade 2 Moderate; minimal, local, or noninvasive intervention (e.g., packing, cautery) indicated; limiting age-appropriate instrumental activities of daily living (ADL)

Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL

Grade 4: Life-threatening consequences; urgent intervention indicated

Grade 5: Death related to AE

7.6.1 NCI Common Terminology for Adverse Events (CTCAE)

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

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

Table 7.6 Evaluating Adverse Events

V4.0 CTCAE Grading	**Grade 1**	Mild; asymptomatic or mid symptoms; clinical or diagnostic observations only; intervention not indicated.
	Grade 2	Moderate; minimal, local or noninvasive intervention

		indicated; limiting age-appropriate instrumental ADL.
	Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation or hospitalization indicated; disabling; limiting self-care ADL.
	Grade 4	Life threatening consequences; urgent intervention indicated.
	Grade 5	Death related to AE
Seriousness	A serious adverse event is any adverse event occurring at any dose or during any use of Merck product that:	
	†**Results in death**; or	
	†**Is life threatening; or** places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred (Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.); or	
	†**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or	
	†**Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization [including hospitalization for an elective procedure] for a preexisting condition which has not worsened does not constitute a serious adverse event.); or	
	†**Is a congenital anomaly/birth defect** (in offspring of subject taking the product regardless of time to diagnosis);or	
	Is a new **cancer;** (that is not a condition of the study) **or**	
	Is an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported within 24 hours to site UCSF CHR and Merck	
	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	
Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units	
Action taken	Did the adverse event cause the Merck product to be discontinued?	
Relationship to test drug	Did the Merck product cause the adverse event? The determination of the likelihood that the Merck product caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test drug and the adverse event based upon the available information. **The following components are to be used to assess the**	

	relationship between the Merck product and the AE; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Merck product caused the adverse event (AE):	
	Exposure	Is there evidence that the subject was actually exposed to the Merck product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
	Time Course	Did the AE follow in a reasonable temporal sequence from administration of the Merck product? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?
	Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors

7.7 Follow-up of Adverse Events

All adverse events will be followed with appropriate medical management until resolved. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event. For selected adverse events for which administration of the investigational drug was stopped, a re-challenge of the subject with the investigational drug may be conducted if considered both safe and ethical by the Investigator.

7.8 Adverse Events Reporting

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, the Committee on Human Research (CHR); 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 Multicenter Phase 2 or 3 Institutional Study at the Helen Diller Comprehensive Cancer Center please refer Appendix 4 Multicenter Institutional Studies.\

7.8.1 Definition of an Overdose for This Protocol and Reporting of Overdose to the study PI and Merck.

For purposes of this trial, an overdose will be defined as any dose exceeding the prescribed dose for pembrolizumab by 20% over the prescribed dose. No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

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

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

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

7.8.2 Serious Adverse Events

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

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

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

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

Any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study that occurs to any subject from the time the consent is signed through 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 to 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] at the time of submission to FDA.

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

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

Although pregnancy and lactation are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them), including the pregnancy of a male subject's female partner that occurs during the trial or within 120 days of completing the trial completing the trial, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier. All subjects and female partners of male subjects who become pregnant must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Such events must be reported within 2 working days to Merck Global Safety. [redacted]

7.9 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 UCSF Committee on Human Research (Institutional Review Board)

The Principal Investigator must report events meeting the UCSF CHR definition of "Unanticipated Problem" (UP) within 10 business days of his/her awareness of the 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 Food and Drug Administration

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

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

- Suspected adverse reaction
- Unexpected
- Serious

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

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

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

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

8.0 Statistical Considerations and Evaluation of Results

This trial will determine whether epigenetic priming may enhance the effects of PD-1 inhibitors in patients with ER+ metastatic breast cancer who have progressed on prior hormone therapy and chemotherapy. The trial will contain three arms. Within each arm we will determine whether epigenetic priming will required prolonged pre-exposure to epigenetic modulators or concomitant administration.

Three arms will be tested, with each independent assessment. Patients will be stratified by prior number of hormonal therapy and chemotherapy, then randomized across arms by Dr. Scott Thomas, UCSF.

8.1 Response rates to chemotherapy in breast cancer are less than 20%. Historical response rates to pembrolizumab and MPDL3280A have been 18% and 19%, respectively, in patients whose tumors are PD-L1 positive. Hence, we expect the response rate for unselected patients and patients with no PD-L1 expression would be 10% or less. In contrast, we anticipate that vorinostat will increase the response rate to 30%Sample Size and Power Estimate

Response rates to hormonal therapy and MTOR or HDAC inhibitors have been reported as 5-20% (19% for VOR-Tam, 6% for entinostat-exemestane, 12% for exemestane-everolimus). Given the recent additions to hormonal therapy this trial will treat a patient population that has received more lines of therapy than these trials, however we are interested in an ORR of >30%.

8.2 For each arm: Using an Optimal Simon's two-stage design (Simon, 1989), the null hypothesis (H_0) that the true response rate is 10% will be tested against a one-sided alternative. In the first stage, 10 patients will be accrued and a decision will be made to continue or stop accrual based on the observed objective response rate (ORR). If there are 0 or 1 objective responses at 24 weeks in these 10 patients, accrual to this arm of the study will be stopped. Otherwise, 19 additional patients will be accrued for a total of n=29. We estimate that each regimen under evaluation will achieve ORR ≥ 30%. This study is designed to have an alpha of 0.0471, and a power of 80.5% to test the null hypothesis H_0: ORR = 10% against an alternative hypothesis, H_A: ORR = 30%, where ORR is defined as CR, PR, or SD ≥ 24 weeks where arms are enrolled independently. Interim Analyses

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 Populations

We will conduct an intention-to-treat analysis of efficacy. All patients who were randomized 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 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. In addition to calculating the ORR, we will calculate the corresponding Agresti-Coull interval 95% confidence interval (CI) (Ref: *Agresti, Alan; Coull, Brent A. (1998). "Approximate is better than 'exact' for interval estimation of binomial proportions". The American Statistician* ***52****: 119–126. doi:10.2307/2685469*). If the lower bound of the 95% CI exceeds 10%, we will reject the null

hypothesis that the regimen is ineffective and conclude that it is sufficiently effective to warrant further study.

8.3.3 Evaluation of Safety

Analyses will be performed for all patients having received at least one dose of study drug. The study will use the NCI CTCAE v4.0.

8.3.4 Analyses of Exploratory Endpoints

8.3.4.1 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 from 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 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 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 downmodulated 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.

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

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

9.2 Institutional Review Board Approval

The protocol, the proposed informed consent form, and all forms of participant information related to the study (e.g., advertisements used to recruit participants) will be reviewed and approved by the UCSF CHR (UCSF Institutional Review Board). Prior to obtaining CHR 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 CHR-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 CHR, any changes to the protocol must be documented in the form of an amendment. The amendment must be signed by the Investigator and approved by PRC and the CHR prior to implementation.

If it becomes necessary to alter the protocol to eliminate an immediate hazard to patients, an amendment may be implemented prior to CHR approval. In this circumstance, however, the Investigator must then notify the CHR in writing within five (5) working days after implementation. The Study Chair and the UCSF study team will be responsible for updating any participating sites.

9.5 Handling and Documentation of Clinical Supplies

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

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

9.6 Case Report Forms (CRFs)

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

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

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

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

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

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 for a Phase 2 or 3 Institutional Study, for additional information.

9.8 Record Keeping and Record Retention

The Principal Investigator 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 Principal Investigator 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 (e.g., signed and dated consent forms and medical records, such as 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, CHR correspondence and approval, signed patient consent forms).

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

In accordance with FDA regulations, the investigator 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.

9.9 Coordinating Center Documentation of Distribution

It is the responsibility of the Study Chair to maintain adequate files documenting the distribution of study documents as well as their receipt (when possible). The HDFCCC recommends that the Study Chair maintain a correspondence file and log for each segment of distribution (e.g., FDA, drug manufacturer, participating sites, etc.).

Correspondence file: should contain copies (paper or electronic) of all protocol versions, cover letters, amendment outlines (summary of changes), etc., along with distribution documentation and (when available) documentation of receipt.

Correspondence log: should be a brief list of all documents distributed including the date sent, recipient(s), and (if available) a tracking number and date received.

At a minimum, the Study Chair must keep documentation of when and to whom the protocol, its updates and safety information are distributed.

10 Protection of Human Subjects

10.1 Protection from Unnecessary Harm

Each clinical site is responsible for protecting all subjects involved in human experimentation. This is accomplished through the CHR mechanism and the process of informed consent. The CHR reviews all proposed studies involving human experimentation and ensures that the subject’s rights and welfare are protected and that the potential benefits and/or the importance of the knowledge to be gained outweigh the risks to the individual. The CHR also reviews the informed consent document associated with each study in order to ensure that the consent

document accurately and clearly communicates the nature of the research to be done and its associated risks and benefits.

10.2 Protection of Privacy

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

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Appendices

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 2 or 3 Institutional Study

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

- Review of subject data
- Review of suspected adverse reactions considered "serious"
- Monitoring every six months (depending on study accrual)
- Minimum of a yearly regulatory audit

Monitoring and Reporting Guidelines

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

All institutional Phase 2 or 3 studies are designated with a moderate risk assessment. The data is monitored twice per year with twenty percent of the subjects monitored (or at least three subjects if the calculated value is less than three).

Adverse Event Review and Monitoring

All grade(s) 3-5 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®, UCSF's Clinical Trial Management System.

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.

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 is determined to be related either to the investigational drug or any research related procedure, the Investigator or or the assigned designee must be notified within 1 business day from the participating site(s) and the Study Chair must then notify the DSMC Chair or qualified alternate within 1 business day of knowledge of this event. The contact may be by phone or e-mail.

Increase in 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, a report should be submitted to the DSMC at the time the increased rate is identified. The report will indicate if the incidence of adverse events observed in the study is above the range stated in the Investigator Brochure or package insert.

If at any time the Study Chair stops enrollment or stops the study due to safety issues, the DSMC Chair and DSMC Manager must be notified within 1 business day via e-mail. The DSMC must receive a formal letter within 10 business days and the CHR must be notified.

Data and Safety Monitoring Committee Contacts

DSMC Chair: [redacted]
Phone:
Email:
Address:
UCSF
San Francisco, CA [redacted]

DSMC Monitors
[redacted]
UCSF Helen Diller Family Comprehensive Cancer Center
San Francisco, CA 94143

* DSMP approved by NCI 09/February2012

Appendix 3 UCSF Policy/Procedure for Required Regulatory Documents for UCSF Investigator-Initiated Oncology Clinical Trials with an Investigator held Investigational New Drug (IND)

Purpose

This policy defines the required Regulatory Documents for Single Site and Multicenter Investigator Initiated Oncology Clinical Trials at the Helen Diller Family Comprehensive Cancer Center (HDFCCC) where the Principal Investigator (PI) holds the IND.

Background

The International Conference on Harmonization (ICH) Good Clinical Practices (GCP) Guidelines define Essential Regulatory Documents as those documents which individually and collectively permit evaluation of the conduct of a trial and the quality of data produced. These documents serve to demonstrate compliance with standards of GCP and with all applicable regulatory requirements. Filing essential documents in a timely manner can greatly assist in the successful management of a clinical trial.

The Regulatory Documents will consist of electronic files in both iMedRIS and OnCore®, as well as paper files in the Regulatory Binders for both the Coordinating Site and the Participating Site(s) in the HDFCCC Investigator Initiated Oncology Clinical Trials.

Procedures

1. HDFCCC Essential Regulatory Documents

Documents Filed in iMedRIS:

- CHR approvals for initial submission of application, all modifications, and continuing annual renewals
- Current and prior approved protocol versions with signed protocol signature page(s)
- Committee for Human Research (CHR) approval letters and Informed Consent Form(s) (ICF)
- Current and prior versions of the Investigator Brochure (IB).
- Serious Adverse Event Reporting
- Protocol Violations and Single Patient Exception (SPE) Reports to CHR with supporting fax documentation

Documents Filed in OnCore®:

- Package Insert (if the study drug is commercial) or Investigator Brochure
- Protocol Review Committee (PRC) approved protocols, protocol amendments and Summary of Changes (SOC)
- Patient handouts
- Screening/enrollment log
- Data and Safety Monitoring Committee (DSMC) monitoring reports
- OnCore® Case Report Form (CRF) completion manual

Documents Filed in Regulatory Binder:

- Completed Food and Drug Administration (FDA) 1572 document with Principal Investigator's signature
- For all Principal Investigators and Sub-Investigators listed on the FDA 1572, will need Financial Disclosure Forms, CVs, MD Licenses, Drug Enforcement Agency (DEA) Licenses, and Staff Training Documents (i.e. Collaborative Institute Training Initiative (CITI), etc.)
- Site Initiation Visit (SIV) minutes and correspondence with participating site(s).
- As applicable, approvals for Biosafety Committee, Radiation Committee, and Infusion Center
- Serious Adverse Event (SAE) reports to CHR.
- MedWatch reporting to FDA
- Delegation of Authority Form
- Drug Destruction Standard Operating Procedure (SOP)
- For all laboratories listed on the FDA 1572, will need CLIA certifications, CAP certifications, lab licenses, CVs of Lab Directors, and laboratory reference ranges

27 April 2012

Appendix 4 Multicenter Institutional Studies

4.1 Data and Safety Monitoring Plan for Multicenter Study (Phase 2 or 3 Institutional Study)

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

- Review of subject data
- Review of suspected adverse reactions considered "serious"
- Monitoring every six months (depending on study accrual)
- Minimum of a yearly regulatory audit

Monitoring and Reporting Guidelines

All institutional Phase 2 or 3 therapeutic studies are designated with a moderate risk assessment. The data is monitored every six months, with twenty percent of the subjects monitored (or at least three subjects if the calculated value is less than three).

The UCSF Coordinating Center provides administration, data management, and organizational support for the participating sites in the conduct of a multicenter clinical trial. The UCSF Coordinating Center will also coordinate quarterly conference calls with the participating sites to communicate the review of adverse events, safety data, and other study matters.

The Principal Investigator at the UCSF Coordinating Center will hold the role of Study Chair. The Study Chair is responsible for the overall conduct of the study and for monitoring its safety and progress at all participating sites. The Study Chair will conduct continuous review of data and subject safety and discuss each subject's treatment at monthly UCSF Site Committee meetings. The discussions are documented in the UCSF Site Committee meeting minutes.

Multicenter communication

The UCSF Coordinating Center provides administration, data management, and organizational support for the participating sites in the conduct of a multicenter clinical trial. The UCSF Coordinating Center will also coordinate, at minimum, quarterly conference calls with the participating sites or more frequently as needed to discuss risk assessment. The following issues will be discussed as appropriate:

- Enrollment information
- Adverse Events (i.e. new adverse events and updates on unresolved adverse events and new safety information)
- Protocol Violations
- Other issues affecting the conduct of the study

Adverse events reporting to the DSMC will include reports from both the UCSF Coordinating Center, as well as the participating sites. The DSMC will be responsible for monitoring all data entered in OnCore® at the UCSF Coordinating Center and the participating sites. The data (i.e., copies of source documents) from the participating sites will be faxed over to the UCSF Coordinating Center prior to the monitoring visits in order for the DSMC to monitor the participating site's compliance with the protocol, patient safety, and to verify data entry.

Adverse Event Review and Monitoring

All grade(s) 3-5 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®, UCSF's Clinical Trial Management System.

All Grade 3-5 adverse events entered into OnCore® will be reviewed on a monthly basis at the UCSF Site Committee meetings. All clinically significant adverse events must be reported to the UCSF Coordinating Center by the participating sites within 10 business days of becoming aware of the event or during the next scheduled quarterly conference call, whichever is sooner. The UCSF 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) from the UCSF Coordinating Center and the participating sites.

In addition, all suspected adverse reactions considered "serious" must be entered in OnCore® and reported to the UCSF Coordinating Center within 1 business day. The suspected adverse reactions considered "serious" will be reviewed and monitored by the Data and Safety Monitoring Committee on an ongoing basis and discussed at the DSMC meeting, which take place every six (6) weeks.

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 is determined to be related either to the investigational drug or any research related procedure, the Study Chair at the UCSF Coordinating Center or the assigned designee must be notified within 1 business day from the participating site(s) and the Study Chair must then notify the DSMC Chair or qualified alternate within 1 business day of this notification. The contact may be by phone or e-mail.

Increase in 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 Study Chair at the UCSF Coordinating Center is responsible for notifying the DSMC at the time the increased rate is identified. The report will indicate if the incidence of adverse events observed in the study is above the range stated in the Investigator Brochure or package insert.

If at any time the Study Chair stops enrollment or stops the study due to safety issues, the DSMC Chair and DSMC Manager must be notified within 1 business day via e-mail. The DSMC must receive a formal letter within 10 business days and the CHR must be notified.

Data and Safety Monitoring Committee Contacts

DSMC Chair: [redacted]
Phone: [redacted]
Email: [redacted]
Address: [redacted]
UCSF
San Francisco, CA [redacted]

DSMC Monitors
[redacted]
UCSF Helen Diller Family Comprehensive Cancer Center
San Francisco, CA 94143

* DSMP approved by NCI 09/February2012

4.2 UCSF Policy/Procedure for Required Regulatory Documents for a UCSF Multicenter Investigator-Initiated Oncology Clinical Trials with an Investigator held Investigational New Drug (IND)

Purpose

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The Regulatory Documents will consist of electronic files in both iMedRIS and OnCore®, as well as paper files in the Regulatory Binders for both the Coordinating Site and the Participating Site(s) in the HDFCCC Investigator Initiated Oncology Clinical Trials.

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- Delegation of Authority Form
- Drug Destruction Standard Operating Procedure (SOP)
- For all laboratories listed on the FDA 1572, will need CLIA certifications, CAP certifications, lab licenses, CVs of Lab Directors, and laboratory reference ranges

27 April 2012