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TITLE: A phase I/II study of pembrolizumab and vorinostat in patients with immune therapy naïve and immune therapy pretreated Stage IV NSCLC

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1.0 TRIAL SUMMARY

Abbreviated Title	A phase I/II study of pembrolizumab and vorinostat in patients with immune therapy naïve and immune therapy pretreated Stage IV NSCLC
Trial Phase	I/II
Clinical Indication	Stage IV NSCLC, ECOG 0-1 patients who are immunotherapy naïve and immune- therapy pretreated. Second line or greater.
Trial Type	phase I/randomized phase II
Type of control	Pembrolizumab for the randomized phase II portion.
Route of administration	Pembrolizumab IV Vorinostat PO
Trial Blinding	Open Label
Treatment Groups	Phase I: Vorinostat dose escalation. Phase Ib: Vorinostat Ib expansion. Randomized Phase II: Arm A (pembrolizumab alone), Arm B (pembrolizumab plus vorinostat).
Number of trial subjects	Total=108 Phase I dose escalation: 12 Phase Ib: 18 Randomized phase II: 78
Estimated enrollment period	18 months
Estimated duration of trial	24 months
Duration of Participation	24 months

2.0 TRIAL DESIGN

2.1 Trial Design

We propose a phase I/randomized phase II clinical trial of pembrolizumab and vorinostat in ECOG 0-1 patients with immune therapy naïve and immune therapy pretreated locally advanced or metastatic NSCLC who have progressed through one prior line of therapy (**Figure 1**). The study would begin with a phase I dose escalation utilizing the modified continuous reassessment method (O'Quigley, Pepe, & Fisher, 1990). This would be followed by a phase I expansion at the maximum tolerated dose (MTD) in 18 NSCLC patients who have been previously treated with anti-PD-1 or anti-PD-L1 therapy. In parallel, a separate phase II arm will randomize 78 patients to a pembrolizumab alone group and a pembrolizumab plus vorinostat group.

2.2 Trial Diagram

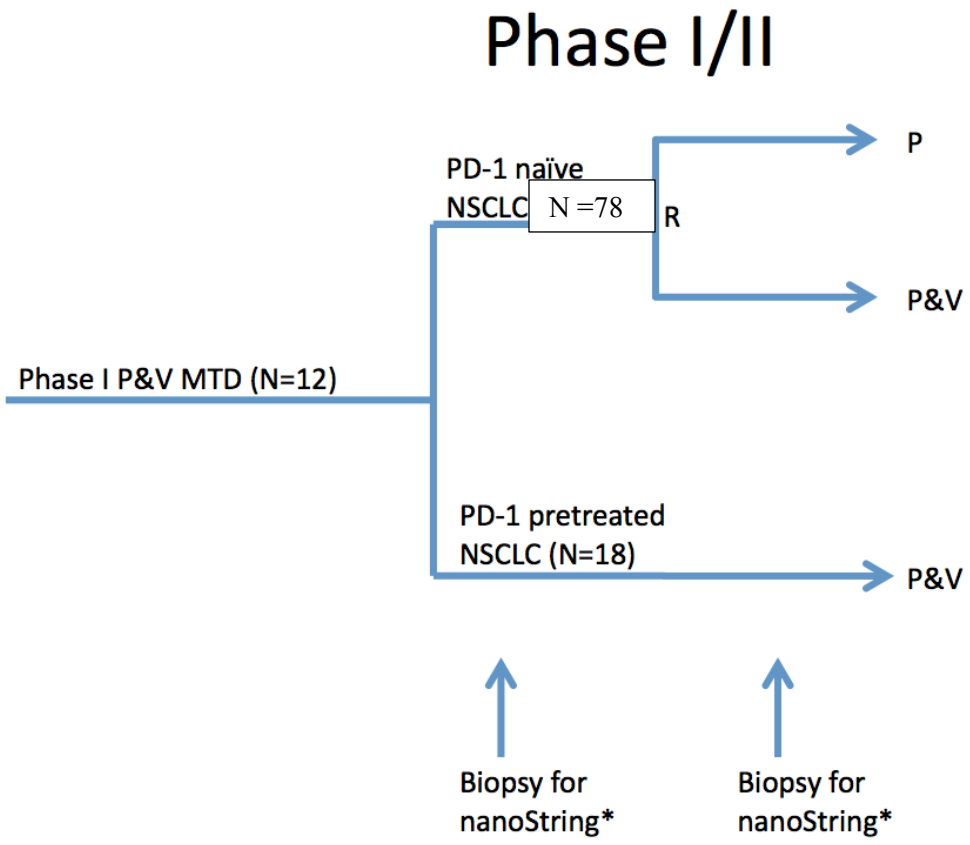


Figure 1. Clinical trial schema. *Pre-treatment and post-treatment biopsies will be obtained in both the phase Ib expansion and the randomized phase II patients. R (Randomization), P (Pembrolizumab), V (Vorinostat), MTD (maximum tolerated dose).

3.0 OBJECTIVES & HYPOTHESES

3.1 Primary Objectives & Hypotheses

Phase 1 Escalation:

Primary Objective: To determine the safety, tolerability and feasibility of concurrent administration of vorinostat and Pembrolizumab.

Hypothesis: Concurrent administration of vorinostat and Pembrolizumab will be safe, tolerable, and feasible.

Phase 1b Expansion (Single Arm, Pre-treated Cohort):

***Primary Objective*:** To determine whether concurrent administration of vorinostat and Pembrolizumab will be effective in NSCLC patients who have been previously exposed to anti-PD-1 or anti-PD-L1 therapy.

Hypothesis: Concurrent administration of vorinostat and Pembrolizumab will be effective in NSCLC patients who have been previously treated with anti-PD-1 or anti-PD-L1 therapy.

Phase II (Randomized, Treatment Naïve Cohort):

Primary Objective: To determine whether concurrent administration of vorinostat and Pembrolizumab is more effective than Pembrolizumab alone.

Hypothesis: Concurrent administration of vorinostat and Pembrolizumab will result in a higher response rate and progression-free survival (PFS) than Pembrolizumab alone.

3.2 Secondary Objectives & Hypotheses

Secondary Objectives (Phase 1 expansion and phase II Arms A and B):

1. To determine immunogenicity molecular profiles that correlate with outcome measures.
2. To determine immunogenicity profiles that correlate with resistance to therapy.
3. To examine and model the mechanisms of resistance to immunotherapy available to cancer cells and the eco-evolutionary dynamics that govern proliferation of the resistant phenotypes.

Secondary Hypotheses (Phase 1 expansion and Phase II Arms A and B):

1. High immunogenicity (High-IG) profiles in pre-treatment biopsies will predict for anti-PD-1+/-vorinostat responsiveness in the Phase I expansion cohort.
2. High or Low immunogenicity (High/Low-IG) profiles will result in a higher response rate in the anti-PD-1+vorinostat therapy group than in the anti-PD1 treatment alone

group in the phase II cohort.
3. During/Post-treatment biopsies we will find that vorinostat combined with anti-PD1 treatment will enhance IG profiles compared to anti-PD1 treatment alone in the Phase I expansion cohort and the phase II cohort.

4.0 BACKGROUND & RATIONALE

4.1 Background

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

4.1.1 *Pharmaceutical and Therapeutic Background*

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

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an Ig superfamily member related to CD28 and CTLA-4 which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2). The structure of murine PD-1 has been resolved. PD-1 and family members are type I transmembrane glycoproteins containing an Ig Variable-type (V-type) domain responsible for ligand binding and a cytoplasmic tail which is responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM). Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3ζ, PKCθ and ZAP70 which are involved in the CD3 T-cell signaling cascade. The mechanism by which PD-1 down modulates T-cell responses is similar to, but distinct from that of CTLA-4 as both molecules regulate an overlapping set of signaling proteins. PD-1 was shown to be expressed on activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B-cells, T regs and Natural Killer cells. Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells. The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types, including non-hematopoietic tissues as well as in various tumors . Both ligands are type I transmembrane receptors containing both IgV- and IgC-like domains in the extracellular region and contain short cytoplasmic regions with no known signaling motifs. Binding of either PD-1 ligand to PD-1 inhibits T-cell activation triggered through the T-cell receptor. PD-L1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments.

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

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

4.1.2 *Preclinical and Clinical Trial Data*

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

4.2 Rationale

4.2.1 *Rationale for the Trial and Selected Subject Population*

The World Health Organization estimated that 1.6 million people died of lung cancer in 2012 (Ferlay et al., 2014). Phase I clinical trials have shown that antibody mediated blockade of either PD-L1 or PD-1 can lead to durable tumor regression in about 20% of patients with advanced non-small cell lung cancer (NSCLC) (Brahmer et al., 2012; Edward B Garon, 2013, 2014; Ghandi, 2014; Suzanne L. Topalian et al., 2012). The pre-clinical and clinical data outlined below indicate that histone deacetylase inhibitors (HDACi) may enhance the efficacy of immune checkpoint inhibition (Juergens et al., 2011; Kelly et al., 2005; Kelly et al., 2003; Ma et al., 2013; Schrump et al., 2008; Vansteenkiste et al., 2008; Wrangle, 2013; Wrangle et al., 2013).

Pembrolizumab (MK3475; Keytruda) in Lung Cancer.

Many studies have evaluated the PD-1/PD-L1 inhibitors in the treatment of advanced stage NSCLC. In summary, overall response rates were ~18% with indications that (1) responses were durable and (2) PD-L1 positivity played a role in response (Brahmer et al., 2012; S. L. Topalian et al., 2012). Immune-related toxicities were seen with both compounds, including pneumonitis at a rate of 3% with the PD-1 inhibitor (Brahmer et al., 2012). Most of these adverse events improved with drug cessation and treatment with glucorticocorticoids/endocrine therapy replacement where appropriate.

In October 2013 and April 2014, respectively, Dr. Garon et al. and Dr. Leena Gandhi et al. presented the results of a phase I study of pembrolizumab (PD-1 inhibitor) in patients with advanced stage NSCLC refractory to 2 lines of prior treatment (Edward B Garon, 2013; Ghandi, 2014). Thirty-eight patients were enrolled. The overall objective response rate was 24% using investigator-assessed immune-related response criteria (irRC). Six of 9 (67%, 95% CI 30-93%) patients with PD-L1 high tumors responded to therapy versus 0/22 (0%, 95% CI 0-15%) patients with PD-L1 low tumors. The most common drug-related adverse

events were rash, pruritus, and fatigue (16% each), and diarrhea (13%). The only grade 3/4 event was one patient who developed grade 3 pulmonary edema. There were no drug-related deaths.

In June 2014, Dr. Garon et al. presented preliminary results from KENOTE-001, a phase I study that randomized 217 patients with known PD-L1 status to pembrolizumab 10mg/kg every 2 weeks (Q2W) and pembrolizumab 10mg/kg every 3 weeks (Q3W) (Edward B Garon, 2014). The overall response rate (ORR) in all patients was 18% (95% CI 13-24%) by irRC and 20% (95% CI 15-26%) by RECIST v1.1. Patients with PD-L1 expressing tumors had ORR of 19% (95% CI 14-26%) by irRC and 23% (16-30%) by RECIST. Patients with PD-L1 negative tumors had ORR of 13% (95% CI 4-27%) by irRC and 9% (2-23%) by RECIST. At the interim analysis, there was no statistical difference in response rates in the different dosage groups. The most common drug–related adverse events included fatigue (13%), decreased appetite (6.5%), arthralgia (6.1%), pruritis (5.4%), and pyrexia (3.6%) and most of these were grade 1/2. Six percent of patients had grade 3/4 drug-related adverse events. Four patients (2 patients in each schedule) developed grade 3/4 pneumonitis.

Updated results of KEYNOTE-001 were recently published by Garon et al. and showed that the objective response rate among all patients was 19.4% (95% CI, 16.0-23.2) and the median duration of response was 12.5 months (range, 1.0-23.3), median PFS 3.7 months (95%CI, 2.9-4.1), and OS 12.0 months (95% CI, 9.3-14.7)(E. B. Garon et al., 2015). The response rate in patients with at least 50% of tumor cells staining positive for PD-L1 was 45.2% (95% CI, 33.5-57.3), median PFS 6.3 months (95% CI, 2.9-12.5), and median OS was not reached (95% CI, 13.7 to not reached). PD-L1 expression in at least 50% of tumor cells correlated with better efficacy of pembrolizumab; however, it is important to note that 16.5% (95% CI, 9.9-25.1) of patients with 1-49% PD-L1 staining responded and 10.7% (95% CI, 2.3-28.2%) of patients with <1% PD-L1 staining also responded. Of the 42 patients treated in the first-line setting, those with a TPS of 1-49%, 5/26 (19.2%) achieved an ORR while in the TPS ≥ 50% group, 8/16 (50%) achieved and objective response. Pembrolizumab was FDA approved in 2016 for first-line NSCLC PD-L1 ≥50 %.

The phase 1/2 KEYNOTE 021 study comparing pembrolizumab plus chemotherapy to pembrolizumab alone was recently presented at ESMO 2016. It demonstrated an improvement in OS and PFS of the triplet compared to the doublet (Langer et al, ESMO 2016). Based on these results carboplatin, pemetrexed plus pembrolizumab was submitted to the FDA as a regimen for first line, Non-squamous NSCLC regardless of PDL1 status. .

Vorinostat in Lung Cancer.

Suberoylanilide hydroxamic acid (SAHA, vorinostat) is an orally active, small molecule inhibitor of histone deacetylase (HDACi). Clinical trials have shown that daily oral vorinostat is safe and tolerable and has a broad range of clinical activity in advanced solid tumors.

Vansteenkiste et al. conducted a phase II trial of oral vorinostat in 16 patients with breast cancer (3 patients), NSCLC (10 patients), and colorectal cancer (3 patients). Patients were treated with oral vorinostat 200mg BID, 300mg BID, or 400mg BID for 14 days on, 7 days off on a 21-day cycle. Dose-limiting toxicities occurred in a total of 6 patients at both the 300mg BID and 400mg BID doses and included weight loss, asthenia, thrombocytopenia, nausea, vomiting, and anorexia. Grade 3/4 toxicities included thrombocytopenia (50%), anemia (12%), asthenia (12%), nausea (12%), and anorexia (6%). No dose limiting toxicities

occurred at the 200mg BID dose level. Although treatment duration was short and TTP was 33.5 days, 6/10 patients with NSCLC had a best response of stable disease by RECIST (Vansteenkiste et al., 2008). Kelly et al. conducted a phase I study that enrolled 50 patients with solid tumors and 23 patients with hematologic malignancies. The maximum tolerated dose was vorinostat 400mg daily or 200mg bid for continuous daily dosing and 300mg bid for 3 of 7 consecutive days. In addition to the dose-limiting toxicities outlined in the prior trial, one patient had elevation of liver enzymes. Only two patients with lung cancer were enrolled in that study; there were two patients with partial responses (laryngeal cancer and mesothelioma) (Kelly et al., 2005). Ma et al. studied vorinostat in a preclinical model with a window of opportunity trial in 15 patients with early-stage lung and esophageal cancers (Ma et al., 2013). Vorinostat 400mg daily was given for 2-9 days and patients had pre-therapy and post-therapy biopsies of target lesions. The study included 10 evaluable patients (8 with lung adenocarcinoma, one with lung squamous cell cancer, and one with esophageal adenocarcinoma). Eight of 9 lung cancer post-treatment biopsies exhibited either acute or chronic inflammation or necrosis when compared to pre-treatment biopsies. Additionally, there was evidence of CD8 positive tumor infiltrating lymphocytes in the post-treatment tissue, supporting the theory that vorinostat acts as a biologic effector of tumor immunogenicity.

Vorinostat has also been safely combined with chemotherapy. For example, Ramalingam et al. combined vorinostat with carboplatin/paclitaxel in 28 patients with advanced malignancies including 19 patients with NSCLC (Ramalingam et al., 2007). The maximum tolerated doses of vorinostat were 400mg daily for 14 of 21 days or 300mg bid for 7 of 21 days. Ten patients with NSCLC had partial responses and 4 had stable disease.

These data show that the toxicities of vorinostat and pembrolizumab do not have substantial overlap. Cytopenias occur in relation to vorinostat. Low incidences of anorexia and nausea occur with both medications.

HDAC inhibitors and PD-1 blockade– Preclinical experience.

Previous studies have demonstrated that increased tumor expression of T cell chemokines, such as CCL5 and CXCL10, is associated with a better response to immunotherapy. Furthermore, expression of T cell chemokines is strongly and positively associated with increased T cell infiltration and improved patient survival (Beg, Khan, & Antonia, 2013; Ji et al., 2012; Ulloa-Montoya et al., 2013). Therefore, enhancement of expression of T cell chemokines may augment response to PD-1 blockade immunotherapy. Recent pre-clinical work in the laboratory of Amer Beg, Ph.D., at the Moffitt Cancer Center showed that HDACi emerged as the only class of agents in a 97-drug screen of FDA-approved oncology agents capable of inducing expression of multiple T cell chemokines, including CCL5, CXCL9, and CXCL10. The ability to induce T cell chemokines was evident with several HDACi, including romidepsin and vorinostat (Figure 2), and in multiple mouse and human lung cancer cell lines and primary tumor specimens (data not shown). HDACi's ability to induce T cell chemokine expression was dependent on both JAK-STAT and NF-kB pathways. We used the HDACi romidepsin to study in vivo effects on lung tumor growth. HDACi treatment of mice bearing LKR tumors did not substantially cause tumor shrinkage but significantly reduced growth ($p<0.0001$; final tumor volume) (Figure 3). Importantly, this effect of HDACi was completely T cell dependent (Figure 3). LKR tumor cells had low cell surface expression of PD-LI but which was substantially increased by IFN-g (not shown). PD-1 blockade with mAb reduced tumor growth but rarely induced rejection (Figure 3, 4). However, when PD-1

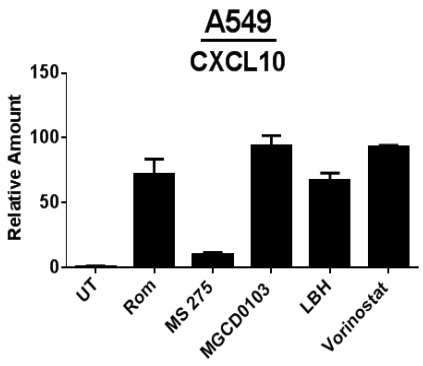
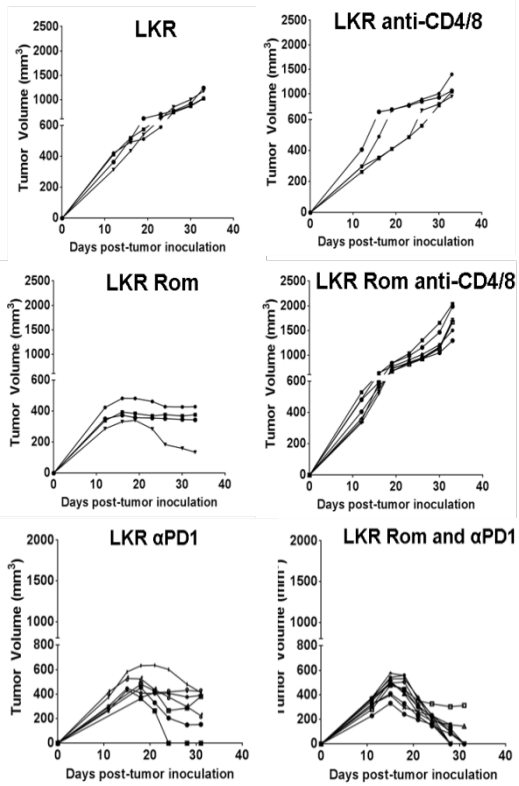


Figure 2: CXCL10 mRNA expression was determined in the human lung cancer cell line A549 following treatment with 30nM romidepsin, 500nM MS275, 1μM MGCD0103, 100nM LBH-589, and 10μM vorinostat for 24h.



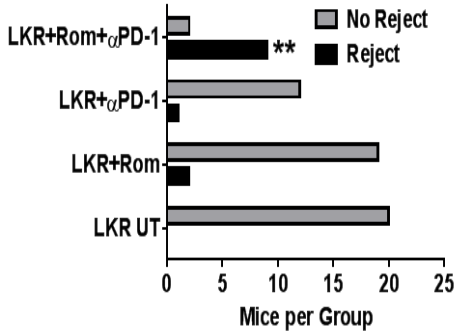
blockade was combined with HDACi, 9 out of 11 mice demonstrated complete tumor rejection (Figures 3 and 4). Importantly, HDACi anti-tumor response correlated with T cell chemokine induction in tumors and greater presence of tumor-infiltrating lymphocytes (TILs). We next used a mouse tumor model (344SQ) that was ***resistant*** to anti-PD-1 treatment. Importantly, PD-1 blockade combined with HDACi significantly reduced growth of these tumors compared to untreated (p=0.0003), anti-PD-1 alone (p=0.01), or HDACi (p=0.004) alone treated mice. These results indicate that HDACi not only enhanced anti-tumor response against PD-1 blockade sensitive tumors (LKR), but also induced response against PD-1 blockade ***resistant*** tumors (344SQ). While in vivo pre-clinical data were generated with the HDACi romidepsin, based on virtually identical in vitro effects of different HDACi, we believe multiple HDACi are likely to have similar activity in vivo.

HDAC inhibitors and PD-1 blockade: Clinical experience.

In a phase I/II trial of 5-azacitadine in combination with entinostat in 19 patients with advanced NSCLC, one patient had a complete

Figure 3: 129 mice were inoculated s.c. with 10^6 LKR, after which they were treated with 2mg/kg romidepsin on days 14,16,18, with or without 300μg/mouse anti-PD-1 antibody on days 15,17,19 as indicated. Tumor growth over indicated time periods is shown. Each line represents a single mouse.

Figure 4: Combined results from 2-3 independent experiments were used to determine significance of reject or no reject outcomes by Fisher Exact Test. The different treatment groups are indicated (LKR UT, n=20; LKR Romidepsin, n=21; LKR anti-PD1, n=13; LKR Romidepsin and anti-PD-1, n=11) and p values were determined compared to the untreated group; LKR Romidepsin: p=0.4878; LKR anti-PD-1: p=0.3939; LKR Romidepsin and anti-PD-1: p<0.0001.



response and another had a partial response. Four patients had partial responses after subsequent therapy and one of those patients was treated with anti-PD-1 (Juergens et al., 2011). In a phase I study, 5 patients were treated with a combination of 5-azacitadine and entinostat prior to being treated with anti-PD-1 or anti-PD-L1 therapy. Three patients had partial responses and two had stable disease by RECIST criteria (Wrangle, 2013). These data necessitate rationally designed clinical trials utilizing concurrent HDACi and immune therapy with engrained biomarker analysis.

PD-L1 as a biomarker.

Tumor PD-L1 expression by immunohistochemistry may enrich for response to anti-PD-1 therapy; however, PD-L1 negative tumors also respond to anti-PD-1 therapy (Edward B Garon, 2014; Wolchok et al., 2013). Interferon-gamma induces PD-L1 expression in tumor cells, and PD-L1 at the tumor cell surface co-localizes with TILs (Taube et al., 2012). In patients with metastatic melanoma, expression of PD-L1 also predicts for longer overall survival (Taube et al., 2012). The molecular underpinnings of PD-L1 expression on tumor cells are poorly understood and would likely provide insight into mechanisms of anti-PD-1 therapy and potential predictive biomarkers. Apart from PD-L1 status, more sensitive biomarkers are needed both to predict response and also to shed insight into the mechanism of anti-PD-1 resistance. As outlined below, a more robust assessment of immunotherapy-permissive tumor microenvironment may better predict response to anti-PD-1 therapy than PD-L1 expression.

An NF-kB gene expression signature is associated with an immune-active tumor microenvironment.

The presence of T cells in tumors is associated with immune surveillance and improved patient survival. We recently investigated whether in addition to known pro-tumor functions, NF-kB activity in cancer cells is also associated with T cell-mediated anti-tumor responses (Hopewell et al., 2013). We found that, in tumors rendered immunogenic by model antigen expression or following administration of anti-tumor vaccines, high NF-kB activity leads to tumor rejection and/or growth suppression. NF-kB regulated T cell chemokines played a key role in lung tumor rejection in mice. To investigate NF-kB function in human lung tumors, we generated a novel gene expression signature to determine NF-kB activity in lung cancer cells (Hopewell et al., 2013). Importantly, overall lung tumor NF-kB activity was strongly associated with T cell infiltration but not with cancer cell proliferation. These results therefore indicate that a predominant effect of NF-kB activity in both murine and human lung cancer is to mediate immune surveillance and promote anti-tumor T cell responses (Hopewell et al., 2013).

While there are few, if any, reliable biomarkers available to predict the response to immunotherapy, many studies suggest that an “immune-active microenvironment” before therapy is associated with response (Ji et al., 2012; Ulloa-Montoya et al., 2013). Based on our findings, we believe that high NF-kB activity in tumors can predict the presence of an immune-active microenvironment permissive to anti-PD-1 immunotherapy. Using the NanoString platform (see below), we will determine association between the NF-kB signature and response to PD-1 blockade alone and in combination with vorinostat.

Nanostring Technology

Whereas microarrays require higher quality RNA that is not easily obtained from formalin-fixed paraffin-embedded tissue (FFPET), the NanoString nCounter allows for high yield and efficient collection of gene expression data from FFPET without the need for a nucleotide amplification step (Geiss et al., 2008; Ullal et al., 2014). Recently, a 20-gene expression profile called Lymph2Cx was used to accurately identify cell-of-origin categories in diffuse large B-cell lymphoma (DLBCL) using NanoString on FFPET (Scott et al., 2014). Another NanoString-based approach is the PAM-50 risk of recurrence score (proSigna), which is an FDA-approved prognostic tool that helps clinicians and patients prognosticate the 10-year risk of distant recurrence in early breast cancer (Dowsett et al., 2013; Gnant et al., 2014). The proSigna test can be performed within 72 hours at local qualified laboratories (package insert, http://prosigna.com/downloads/). Nanostring technology is therefore a clinically robust platform for molecular correlative studies. Importantly, NanoString allows simultaneous detection of expression of up to 800 genes. We will use NanoString to determine expression of key gene expression signatures and additional genes associated with an immune-active tumor microenvironment. Depending on biopsy tissue availability, we will perform RNA-sequencing analysis to answer many of the same questions discussed above in NanoString studies. The experiments will be run on the nCounter in the Moffitt Cancer Center Molecular Genomics Core facility.

Summary

The pre-clinical data from Amer Beg's laboratory here at Moffitt, in addition to the clinical data summarized above, provide sound rationale for a clinical trial evaluating the combination of HDAC inhibition with PD-1 inhibitors in patients with NSCLC and the assessment of potential of predictive biomarkers that go beyond PD-L1 status in tumor tissue. This will open the opportunity to improve the outcomes of patients with a terminal cancer.

4.2.2 *Rationale for Dose Selection/Regimen/Modification*

An open-label Phase I trial (Protocol 001) is being conducted to evaluate the safety and clinical activity of single agent pembrolizumab. The dose escalation portion of this trial evaluated three dose levels, 1 mg/kg, 3 mg/kg, and 10 mg/kg, administered every 2 weeks (Q2W) in subjects with advanced solid tumors. All three dose levels were well tolerated and no dose-limiting toxicities were observed. This first in human study of pembrolizumab showed evidence of target engagement and objective evidence of tumor size reduction at all dose levels (1 mg/kg, 3 mg/kg and 10 mg/kg Q2W). No MTD has been identified to date. 10.0 mg/kg Q2W, the highest dose tested in PN001, will be the dose and schedule utilized in Cohorts A, B, C and D of this protocol to test for initial tumor activity. Recent data from other clinical studies within the pembrolizumab program has shown that a lower dose of pembrolizumab and a less frequent schedule may be sufficient for target engagement and clinical activity.

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

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

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

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

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

Thus, the phase I dose escalation will include a fixed dose of Pembrolizumab 200mg IV every 3 weeks and escalating doses of vorinostat (**Table 1**) to determine the MTD to be used in the expansion group and the randomized phase II portion of the trial. Once a MTD is determined, patients can start on the phase Ib expansion and phase II portions of the trial. Cycle 1, day 1 will start with Pembrolizumab concurrent with continuous daily oral therapy with vorinostat.

Table 1: Vorinostat dose levels in phase I dose escalation phase.

Dose Level	Vorinostat Dose	Pembrolizumab Dose
-1	100mg PO Daily	200mg IV Q3 weeks
1	200mg PO Daily	200mg IV Q3 weeks
2	400mg PO Daily	200mg IV Q3 weeks

4.2.3 *Rationale for Endpoints*

Safety, tolerability, response rate, disease control rate, progression-free survival, duration of response, and overall survival will be interrogated as feasibility and efficacy endpoints.

4.2.3.1 Efficacy Endpoints

In addition to a baseline scan, confirmatory scans will be obtained 4-6 weeks following initial documentation of objective response. Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1)(Eisenhauer et al., 2009). Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used (Schwartz et al., 2009).

Patients who are found to have stable disease (SD), partial response (PR), or complete response (CR) will continue on study until evidence of disease progression, intolerance, or withdrawal from study. Response rate, overall survival, and progression-free survival will be determined. Subjects with progressive disease by RECIST 1.1 but without rapid clinical deterioration may continue to be treated at the discretion of the investigator.

The efficacy analysis will be based on the treated Population which includes all subjects who receive any dose of either investigational product. The following efficacy endpoints will be analyzed.

- Objective response is defined as confirmed CR or confirmed PR based on modified RECIST guidelines version 1.1. The ORR will be estimated by calculating the proportion of subjects who achieve OR; the 80% CI and 95% CI for the OR rate will be estimated using the exact binomial distribution.
- Disease control is defined as CR, PR, or SD based on RECIST guidelines version 1.1 with modifications. The disease control rate (DCR) will be estimated by the proportion of subjects who achieve DC, and its 80% CI and 95% CI will be estimated using the exact binomial distribution.

• Progression-free survival will be measured from the start of treatment with pembrolizumab and vorinostat until the documentation of disease progression or death due to any cause, whichever occurs first. For subjects who are alive and progression-free at the time of data cut-off for analysis, PFS will be censored at the last tumor assessment date. The Kaplan-Meier method (Kaplan and Meier, 1958) will be used to estimate the PFS curve and the PFS rate at time points of interest.
• Duration of response is defined as the duration from the first documentation of OR to the first documented disease progression or death due to any cause, whichever occurs first. For subjects who are alive and progression-free at the time of the data cut-off for the analysis, DoR will be censored at the last tumor assessment date. The DoR will only be evaluated for the subgroup of subjects with an OR and will be calculated using the Kaplan-Meier method.
• Overall survival will be determined as the time from the start of treatment with pembrolizumab and vorinostat until death due to any cause. For subjects who are alive at the time of data cut-off, OS will be censored on the last date when subjects are known to be alive. The Kaplan-Meier method will be used to estimate the OS curve and the OS rate at time points of interest.

4.2.3.2 Disease Parameters

- *Measurable disease*. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded for non-nodal lesions and short axis for nodal lesions) as ≥20 mm by chest x-ray, as ≥10 mm with CT scan, or ≥10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters). **Note:** Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable. If the investigator thinks it appropriate to include them, only lesions that have clearly shown disease progression since prior irradiation will be considered or allowed.
- *Malignant lymph nodes*. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.
- *Non-measurable disease*. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥ 10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable. **Note:** Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts. “Cystic lesions” thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.
- *Target lesions.* All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as *target lesions* and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does

not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

- *Non-target lesions*. All other lesions (or disease sites) including any measurable lesions over the 5 target lesions, should be identified as *non-target lesions* and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

4.2.4 *Methods for Evaluation of Measurable Disease*

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should 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 unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

- *Clinical lesions:* Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥10 mm diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.
- *Chest x-ray:* Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.
- *Conventional CT and MRI:* This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g., for body scans). Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI that greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

4.2.5 *Response Criteria*

4.2.5.1 Evaluation of Target Lesions

- Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
- Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.
- Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).
- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

4.2.5.2 Evaluation of Non-Target Lesions

- Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis). **Note:** If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.
- Non-CR/Non-PD: 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. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.
- Although a clear progression of “non-target” lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

4.2.5.3 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 2. For Patients with Measurable Disease (i.e., Target Disease)

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

*See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.

**Only for non-randomized trials with response as primary endpoint.

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

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration."* Every effort should be made to document the objective progression even after discontinuation of treatment.

Table 3. For Patients with Non-Measurable Disease (i.e., Non-Target Disease)

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

* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions

can be measured is not advised

4.2.6 *Progression-Free Survival*

Progression free survival (PFS) is defined as the time from start of treatment (Cycle 1, Day 1) until the date of objective disease progression or death (by any cause in the absence of progression) regardless of whether the patient withdraws from therapy or receives another anti-cancer therapy before progression. Clinical deterioration in the absence of radiographic evidence is not considered progression for purposes of determining PFS. Subjects who die without a reported prior progression will be considered to have progressed on the date of their death. Subjects who did not progress or die will be censored on the date of their last evaluable tumor assessment. Subjects who did not have any on study tumor assessments and did not die will be censored on the date they were first treated. Subjects who started any palliative local therapy or subsequent anti-cancer therapy without a prior reported progression will be censored at the last evaluable tumor assessment prior to initiation of the palliative local therapy or subsequent anti-cancer therapy, whichever procedure occurred first.

The PFS time will always be derived based on scan/assessment dates not visit dates.

RECIST version 1.1 assessments/scans contributing towards a particular visit may be performed on different dates. The following rules will be applied:

- Date of progression will be determined based on the earliest of the dates of the component that triggered the progression

- When censoring a patient for PFS the patient will be censored at the latest of the dates contributing to a particular overall visit assessment.

4.2.7 *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 progressive disease is objectively documented. If a patient does not progress following a response, then their duration of response will use the PFS censoring time.
- 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, including the baseline measurements.

4.2.8 *Objective Response Rate*

ORR is defined as the number of subjects whose best confirmed objective response (BOR) is a CR or PR, divided by the number of subjects who received at least one dose. BOR is defined as the best response designation, as determined by the RECIST v1.1, recorded between baseline and the date of objectively documented progression per RECIST 1.1 or the date of initiation of palliative local therapy or the date of initiation of subsequent anticancer therapy, whichever occurs first. For subjects without documented progression or palliative local therapy or subsequent anti-cancer therapy, all available response designations will contribute to the BOR determination. The final analysis of ORR will take place at the time of PFS.

4.2.9 *Overall Survival*

OS is defined as the duration of time from the date for first treatment (Cycle 1 Day 1) to the date of death. A subject who has not died will be censored at last known date alive.

4.2.10 *Missing Assessments and Not Evaluable Designation*

When no imaging/measurement is done at all at a particular time point, the subject is not evaluable (NE) at that time point. If only a subset of lesion measurements can be made at an assessment, the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not have changed the assigned time-point response.

4.2.11 *Treatment Beyond Progression*

Accumulating evidence indicates a minority of subjects treated with immunotherapy may derive clinical benefit despite initial evidence of PD.

Subjects will be permitted to continue treatment beyond initial RECIST v1.1 defined PD as long as they meet the following criteria:

- Investigator-assessed clinical benefit and subject is tolerating study drug.
- No evidence of significant clinical decline.
- Subjects will be re-consented with an informed consent document describing any reasonably foreseeable risks or discomforts and other alternative treatment options. A follow-up scan should be performed within six 6 weeks +/- 7 days of original PD to determine whether there has been a decrease in the tumor size, or continued PD. The assessment of clinical benefit should be balanced by clinical judgment as to whether the subject is clinically deteriorating and unlikely to receive any benefit from continued treatment with Pembrolziumab (+ vorinostat for Arm B). If the investigator feels that the subject continues to achieve clinical benefit by continuing treatment, the subject should remain on the trial. The decision to continue treatment should be discussed with sponsor documented in the study records. **For the subjects who continue study therapy beyond progression, further progression is defined as an additional 20% increase in tumor burden from time of initial

PD. This includes an increase in all target lesions and any new measurable lesions. Study therapy should be discontinued if further progression is documented. New lesions are considered measureable at the time of initial progression if the longest diameter is at least 10mm (except for pathological lymph nodes which must have a short axis of at least 15 mm). Any new lesion considered non-measureable at the time of initial progression may become measureable and therefore included in the tumor burden if the longest diameter increases to at least 10 mm (except for pathological lymph nodes which must have a short axis of at least 15 mm). The diameter(s) of any measurable new lesion(s) should be added to the target lesion sum of longest diameters in determining whether the criteria for further progression has been met.

4.2.12 *Biomarker Research*

4.3 Biological sampling procedures

4.3.1 *Immunogenicity sampling and evaluation methods*

Those enrolled on the Phase I (where Tissue allows) or the Phase II randomized study will be required to undergo a core biopsy of a target or nontarget lesion prior to starting treatment and between cycle 1 days 15-21.

The pretreatment biopsy or archival sample needs to have occurred after the most recent line of therapy, and be either an FFPE sample or slide cut within 6 months of the assay for PD-L1

Pharmacodynamic endpoints will then be assessed in the tumor tissue. We will determine whether tumor immunogenicity prior to treatment is associated with the response to pembrolizumab ± vorinostat, and whether vorinostat treatment leads to *greater* enhancement in immunogenicity after treatment. We broadly define tumor immunogenicity to include both T cell presence and the expression of immune response-promoting genes. To this end, we will perform tumor biopsies prior to treatment and again at C1 Day15-21 after initiation of treatment (i.e. on-treatment). NanoString assay will be used to determine expression of potentially important immune function genes, including a recently defined NF-kB gene expression signature in lung cancer cells that is associated with greater T cell presence in human lung adenocarcinoma. An additional key goal is to determine association of pre- or on-treatment expression of other immune checkpoints genes (e.g. BTLA, LAG3, TIM3) with resistance to pembrolizumab ± vorinostat treatment. These important studies can provide a framework to assess how pembrolizumab ± vorinostat modulate the tumor microenvironment, characterize potential utility of biomarkers in response to treatment (e.g. NF-kB activity), and identify resistance mechanisms.

4.3.2 *Biomarker/Pharmacodynamic sampling and evaluation methods*

Molecular studies. The following molecular test results including but not limited to ALK, EGFR, K-ras, ROS-1, PD-L1 status, RET, Met, PTEN, BRAF, PI3K and Her2 neu will be conducted when appropriate or collected when available in the medical record. PD-L1 status by immunohistochemistry and quantitation of tumor infiltrating lymphocytes will be determined on all biopsy specimens.

PD-L1 expression will be measured in all fresh and archival biopsies using the IHC assay based on the anti-PD-L1 monoclonal antibody (most likely the Merck anti-PD-L1 clone 22C3). Positive staining with this assay is currently defined as tumor cell membrane staining at any intensity, analyzed with a cut-off value of ≥ 1% in a minimum number of 100 evaluable cells. Baseline tumor PD-L1 expression will be evaluated for potential association with ORR, PFS, and overall survival (OS).

Further, exploratory correlative studies may be completed based on the additional data obtained including utilization of an advanced DNA platform or additional immune based biomarker analyses. These results would also be correlated with patient outcomes and potentially help to address some of the critical barriers for effective personalized treatment.

Histone acetylation studies on PBMC's. Previous studies have indicated that HDAC inhibitors lead to the acetylation of many molecules including of histone 3 and 4. Biomarker assessments will be made on blood for assessment of pre and post-treatment effects on acetylated histone 3 (H3) and histone 4 (H4), total H3 and H4. Correlative analysis will be performed on the peripheral blood mononuclear cells (PBMC) of all the patients enrolled in the study. This will include flow cytometry based assessment of presence of suppressive cell types such as myeloid-derived suppressor cells (MDSC) and Tregs. In addition, we will determine expression of activation and resistance markers in lymphocytic lineages, including T cells, by flow cytometry and gene expression studies. Plasma will also be collected to determine levels of key cytokines and chemokines. The blood draws will take place pretreatment (either during screening or on C1D1) and during treatment (C1D15+/- 7 days). Peripheral blood mononuclear cells will be isolated from patient blood collected prior to and after initiation of therapy to measure H3 and H4 histone acetylation by western blot analysis by Dr. Amer Beg's lab as previously described Gray et al, CCR, 2014(Gray et al., 2014).

4.3.3 *Eco-evolutionary modeling methods*

Toward secondary objective #3, the following steps will be taken:

The initial step will use available clinical and correlative data to examine (in the context of estimated immune response to therapy) the changes in frequency of subpopulations within each lung cancer on biopsies taken prior to therapy, during therapy, and (where available) at the time of tumor progression. This will be used to parameterize models using (non-spatial) Ordinary Differential Equations of the evolutionary dynamics.

In the second step, we will apply image analytic methods to the existing pathology slides. This will allow development of spatially-explicit mathematical models including Partial

Differential Equation and Agent-based methods to capture the ecological as well as evolutionary dynamics.

A final step involves testing model predictions or exploring hypotheses developed through model simulations by performing additional studies on available samples, for example, obtaining new IHC stains on the pathology slides.

4.3.4 *Archival Tumor Samples and Fresh Tumor Biopsies*

4.3.4.1 Archival tumor samples and Fresh tumor biopsies

Archived tissue will be collected from all patients enrolled on the study. For those enrolled on the phase I escalation portion without available archival tissue, fresh tumor specimens will be collected by image-guided biopsy with onsite pathologic confirmation by a trained cytotech or board certified cytopathologist. Approximately 125 µL of tumor sample is required at baseline for PDL1 testing and to evaluate potentially predictive biomarkers and complete other correlative studies. In addition, patients enrolled on the phase I dose escalation, Phase Ib expansion and randomized phase II portions of the trial will undergo serial biopsies. More specifically, those enrolled on the phase I dose escalation, Phase Ib expansion and Phase II randomized study will be required to undergo a core biopsy of an accessible lesion prior to starting treatment (or collection of archival tissue from after the most recent line of therapy where available) and between cycle 1 day 15-21. The biopsies will be performed under image guidance (including but not limited to CT or ultrasound-guided core biopsies) as determined by the location of tumor and risks associated with each procedure. Fresh tumor biopsies, on-site evaluations for tissue quality will be performed by the cytotechnologist to ensure viable tissue and for collection of adequate tumor sample. Four to 6 core biopsy samples will be collected. At a minimum, 2 will be placed in neutral-buffered formalin and embedded in paraffin wax and two core needle samples will be snap frozen and stored in liquid nitrogen. The tumor collected through these methods will be analyzed to explore whether positive vs negative biomarkers could predict response and resistance to the treatment. Samples will be retained after the clinical study report has been finalized.

4.3.4.2 Molecular Analyses

These correlates will be analyzed using descriptive statistics to compare disease outcome in biomarker positive and negative subsets. In addition, univariate and multivariate analyses will be performed to see whether the markers described above (both as continuous or dichotomous variable) predict for disease outcome (i.e., disease control rate, response and PFS after appropriate adjustment for other prognostic variables).

4.3.4.3 Withdrawal of informed consent for donated biological samples

If a subject withdraws consent to the use of donated samples, the unused samples will be disposed of/destroyed, and the action documented.

The Principal Investigator:

- Ensures that biological samples from that subject, if stored at the study site, are immediately identified, disposed of /destroyed, and the action documented

- Ensures the laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed/destroyed, the action documented and the signed document returned to the study site
- Ensures that the subject is informed about the sample disposal.

Molecular studies

The following molecular test results including but not limited to ALK, EGFR, K-ras, ROS-1, PD-L1 status, RET, Met, PTEN, BRAF, PI3K and Her2-*neu* will be conducted when appropriate or collected when available in the medical record. PD-L1 status by immunohistochemistry and quantitation of tumor infiltrating lymphocytes will be determined on all biopsy specimens.

Pharmacodynamic studies

NanoString Analysis. We will use a customized panel of ~100 genes (Custom Immune Panel) which will include genes in the NF-kB signature (30 genes with highest Principal Component Analysis (PCA) weight), resistance genes, T cell chemokines, T cell genes, HLA genes, co-stimulatory molecules and housekeeping genes (**Table 4**). Using this panel, we will separately evaluate expression by PCA of the NF-kB signature and a 12-gene T cell chemokine signature, which was also generated at Moffitt Cancer Center using bioinformatic gene expression analysis of 14,492 distinct solid tumors.

A key component of NanoString analysis will be to define resistance mechanisms in patients who fail to respond to treatment and those who progress after initially responding. A major mechanism of resistance may be the presence of other “driver” immunosuppressive mechanisms within the tumor microenvironment. These may include additional immune checkpoints (BTLA, LAG3, TIM3, A2AR), suppressive immune cells (Treg, TAMs), immunosuppressive enzymes (IDO, arginase), and/or immunosuppressive cytokines (TGFB, IL-10). NanoString studies will help determine whether pre-treatment and/or on-treatment expression of genes encoding for these additional immunosuppressive pathway components are associated with resistance to treatment. Depending on availability of biopsy samples, we will further determine protein expression of potentially important immunosuppressive molecules by IHC (see below). In patients who initially respond to therapy, there will be an option to also obtain a third biopsy upon progression of disease. Defining presence or emergence of resistance markers in these patients may therefore provide new insights into possible therapeutic strategies for this cohort of patients.

RNA sequencing. RNA sequencing (RNA-seq) can be used for exome wide analysis of gene expression. Depending on biopsy tissue availability, we will perform RNA-seq analysis to answer many of the same questions discussed above in NanoString studies. In addition, RNA-seq can help define new genes that may be associated with response and synergy between pembrolizumab and vorinostat as well as genes whose expression is changed as a result of treatment. If sufficient fresh frozen tissue is available, we will perform RNA-seq instead of NanoString studies.

IHC studies. Biopsy slides (FFPE) will be utilized to determine presence of CD8+ TILs and CD33+ myeloid cells. We will assess association of both cell types in pre-treatment biopsies

with patient response. In addition, we will determine changes in presence of these cell types as a result of treatment. We will also separately assess presence of these cell types in tumor beds and tumor stroma as they may differentially associate with response. Finally, if sufficient tissue is available, we will expand our studies to Vectra panels which rely on immunofluorescence to detect presence of multiple cell types. We will utilize panels which will include, but not limited to, FoxP3 (Treg marker), CK, CD3, CD4, CD8, Granzyme-B (to determine cytolytic activity of T cells), Ki67 (to determine T cell proliferation, which is associated with ongoing anti-tumor activity).

Histone acetylation studies on PBMC's and tumor biopsies.
Previous studies have indicated that HDAC inhibitors lead to the acetylation many molecules including of histone 3 and 4. Biomarker assessments will be made on blood and tumor tissue for assessment of pre and post-treatment effects on but not limited to acetylated histone 3 (H3) and histone 4 (H4), total H3 and H4, and quantitative HDAC assay. Assessments will be made by Western Blot. Correlative analysis will be performed on the peripheral blood mononuclear cells (PBMC) of all the patients enrolled in the study. The blood draws will take place pretreatment (either during screening or on C1D1), during treatment (C1D15) and at progression. We will isolate peripheral blood mononuclear cells from patient blood collected prior to and after initiation of therapy to measure H3 and H4 histone acetylation by western blot analysis.

Shipping information for PBMC and Tissue samples:

Moffitt Cancer Center
Attn: Tissue Core ACQ
12902 Magnolia Drive.
MCC 3040 / Tissue Core
Tampa, FL 33612
813-745-57763

Table 4. Genes in the custom immune panel.

NF-kB Signature	**T cell chemokines**	**T cell marker genes**	**HLA genes**
GBP1	CCL2	CD8A	HLA-A
PSMB9	CCL3	CD4	HLA-B
IRF1	CCL4	CD3E	HLA-C
TAP1	CCL5	CD3G	HLA-DMA
TNFAIP3	CCL8	TRAC	HLA-DMB
CCL5	CCL18	TRBC1	HLA-DOB
PSMB8	CCL21	**DC/APC markers**	HLA-DPA1
IL32	CXCL9	CD80	HLA-DPB1
SH2B3	CXCL10	CD83	
NFKBIE	CXCL11	CD86	
	CXCL12		

OPTN BIRC3 PSME2 ARNTL2 GFPT2 ITGA5 HLA-B ITGAM TAP2 IFIH1 CYLD PLAUR CCL2 MMP9 LAMC2 CTSS LXN RELB G0S2 PARP12	**Resistance genes** BTLA4 LAG3 HAVCR2 ADORA2A IDO1 ARG1 TGFB1 IL10 FOXP3 CTLA4 PDCD1 CD274 PDCD1LG2	**Co-stimulation genes** CD40 CD40LG CD27 CD28 ICOS TNFRSF9 FAS FASLG	HLA-DQA1 HLA-DQB1 HLA-DRA HLA-DRB3 HLA-DRB4 HLA-E HLA-G

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 *Diagnosis/Condition for Entry into the Trial*

1. Histologic or cytologic diagnosis of Stage IV NSCLC

5.1.2 *Subject Inclusion Criteria*

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

1. Be willing and able to provide written informed consent/assent for the trial.
2. Be ≥ 18 years of age on day of signing informed consent.
3. Have measurable disease based on RECIST 1.1.
4. Have archival tissue where available. Those patients enrolled on the phase 1 escalation trial where archival tissue is not available will undergo a fresh biopsy where clinically feasible after discussion with the sponsor.

5. In addition, patients enrolled on the phase 1 dose escalation, phase 1 expansion or Phase II trial must be willing and able to provide tissue from a newly obtained core or excisional biopsy of a tumor lesion. *Newly-obtained is defined as a specimen obtained up to 3 months prior to initiation of treatment on Day 1, and must be obtained after most recent treatment. Subjects for whom newly-obtained samples cannot be provided (e.g. inaccessible or subject safety concern) may submit an archived specimen only upon agreement from the Sponsor.)*

6. Randomized phase II: Tumor proportional score of PD-L1 ≥1%.

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

8. Demonstrate adequate organ function as defined in **Table 5** all screening labs should be performed within 10 days of treatment initiation.

9. Have a histologic or cytologic diagnosis of Stage IV NSCLC.

10. Phase I/IB (Pre-treated): Have progression from at least one prior line of therapy. Maintenance therapy following platinum doublet-based chemotherapy is not considered as a separate regimen of therapy. Subjects who received platinum-containing adjuvant, neoadjuvant or definitive chemoradiation therapy given for locally advanced disease, and developed recurrent (local or metastatic) disease within 6 months of completing therapy are eligible for these arms. Subjects with recurrent disease ≥ 6 months after completing a platinum-containing adjuvant, neoadjuvant or definitive chemoradiation therapy given for locally advanced disease, who also subsequently progressed during or after a systemic regimen given to treat the recurrence, must have received another treatment in the first-line metastatic setting.
11. Randomized Phase II: Be treatment naïve in the stage IV setting, with the exception of patients whose tumors harbor an activating mutation (including but not limited to EGFR, ALK, ROS1) and were previously treated with targeted therapy. Subjects who received platinum-containing adjuvant, neoadjuvant or definitive chemoradiation therapy given for locally advanced disease, and developed recurrent (local or metastatic) disease < 6 months of completing therapy are ineligible for this arm. Subjects with recurrent disease ≥ 6 months after completing a platinum-containing adjuvant, neoadjuvant or definitive chemoradiation therapy given for locally advanced disease, who also subsequently progressed during or after a systemic regimen given to treat the recurrence, are eligible for this arm.
12. Female subjects of childbearing potential should have a negative urine or serum pregnancy within 72 hours prior to receiving the first dose of study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

13. Female subjects of childbearing potential should be willing to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of study medication (Reference Section 5.7.2). Subjects of childbearing potential are those who have not been surgically sterilized or have not been free from menses for > 1 year.

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

Table 5. Adequate Organ Function Laboratory/Test Values

System	Laboratory/Test Value
Hematological	
Absolute neutrophil count (ANC)	≥1,500 /mcL
Platelets	≥100,000 / mcL
Hemoglobin	≥9 g/dL
Renal	
Serum creatinine **OR** Measured or calculated[a] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 X upper limit of normal (ULN) **OR** ≥60 mL/min for subject with creatinine levels > 1.5 X institutional ULN
Hepatic	
Serum total bilirubin	≤ 1.5 X ULN **OR**
	Direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 X ULN **OR** ≤ 5 X ULN for subjects with liver metastases
Albumin	≥2.5 mg/dL
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT) Activated Partial Thromboplastin Time (aPTT)	≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants ≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
Cardiac	
Left ventricular ejection fraction (LVEF)	≥45%
[a]Creatinine clearance should be calculated per institutional standard.	

5.1.3 *Subject Exclusion Criteria*

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

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

2. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy at doses ≥ 10 mg prednisone or any other form of systemic immunosuppressive therapy within 7 days prior to the first dose of trial treatment. Subjects are permitted to use topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). Physiologic replacement doses of systemic corticosteroids are permitted, even if > 10 mg/day prednisone equivalents. A brief course (≤28 days) of corticosteroids for prophylaxis (eg, contrast dye allergy) or for treatment of non-autoimmune conditions (eg, delayed-type hypersensitivity reaction caused by contact allergen) is permitted.

3. Has a known history of TB Disease (Mycobacterium tuberculosis)

4. Hypersensitivity to pembrolizumab, vorinostat or any of its excipients

5. Patients enrolled on the phase II randomized trial, who have had prior treatment with a PD1 or PDL1 inhibitor, anti-CTLA 4 antibody or any other antibody or drug that specifically targets immune checkpoint pathway (i.e. not "immune therapy naïve").

   -Note: For those enrolled in the phase I dose escalation, prior use of a PD1 or PDL1, anti-CTLA4 antibody or any other antibody or drug that specifically targets immune checkpoint pathway is allowed. For those enrolled in the phase IB, prior use of a PD1 or PDL1, anti-CTLA4 antibody or any other antibody or drug that specifically targets immune checkpoint pathway is required. For all patients in all phases, prior use of a vaccine for treatment of cancer is allowed.

6. Patients enrolled in the phase Ib expansion who have never previously been treated with a PD1 or PDL1 inhibitor, anti-CTLA 4 antibody or any other antibody or drug that specifically targets immune checkpoint pathway in the past (i.e. not "pre-treated")

7. Patients who have received thoracic radiation >30Gy within six months of the first dose of pembrolizumab.

8. Patients taking any HDACi other than vorinostat.

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

10. Has had prior chemotherapy within 3 weeks, or targeted small molecule therapy or radiation therapy within 2 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to a previously administered agent.

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

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

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

13. Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least four weeks prior to the first dose of trial treatment and any neurologic symptoms have

returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids in doses greater than 10 mg of prednisone daily (or equivalent) for at least 7 days prior to trial treatment. This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability.

14. Has active autoimmune disease that has required systemic treatment in the past 2 years (i.e. with use of disease modifying agents, corticosteroids in doses greater than 10 mg of prednisone daily (or equivalent) or immunosuppressive drugs). Replacement therapy (eg., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment. Subjects are permitted to enroll if they have vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger.

15. Has an active infection requiring systemic therapy.

16. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, that would substantially increase risk of incurring adverse events (AEs) from the study medications, that would 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.

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

18. 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.

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

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

21. Has received a live vaccine within 30 days of planned start of study therapy.

Note: Seasonal influenza vaccines for injection are generally inactivated flu vaccines and are allowed; however intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines, and are not allowed.

22. Has a history of, or any evidence of activenon-infectious pneumonitis that required or requires steroids.

23. Has evidence of interstitial lung disease

24. Has a history of symptomatic (NYHA class II-IV) heart failure.

5.2 Trial Treatments

The phase I dose escalation will include a fixed dose of Pembrolizumab 200mg IV every 3 weeks and escalating doses of vorinostat (three dose levels) to determine the MTD to be used in the expansion group and the randomized phase II portion of the trial. Once a MTD is determined, the phase Ib expansion and randomized phase two portions of the trial can begin accrual. Cycle 1, day 1 will start with Pembrolizumab concurrent with continuous daily oral therapy with vorinostat.

Table 6. Vorinostat dose levels in phase I dose escalation phase.

Dose Level	Vorinostat Dose, Route, Frequency	Pembrolizumab Dose, Route, Frequency	Use
-1	100mg PO Daily	200mg IV Q3 weeks	Experimental
1	200mg PO Daily	200mg IV Q3 weeks	Experimental
2	400mg PO Daily	200mg IV Q3 weeks	Experimental

Trial treatment should begin within 3 days of randomization or as close as possible to the date on which treatment is allocated/assigned.

5.2.1 *Dose Selection/Modification*

5.2.1.1 Dose Selection

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

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

5.2.1.2 Dose Modification

Adverse events (both non-serious and serious) associated with pembrolizumab exposure may represent an immunologic etiology. These adverse events may occur shortly after the first dose or several months after the last dose of treatment. Pembrolizumab must be withheld for drug-related toxicities and severe or life-threatening AEs as per **Table 7** below. See Section 5.6.1 and Events of Clinical Interest Guidance Document for supportive care guidelines, including use of corticosteroids.

Table 7. Dose Modification Guidelines for Drug-Related Adverse Events

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Discontinue Subject
Diarrhea/Colitis	2-3	Toxicity resolves to Grade 0-1.	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue
AST, ALT, or Increased Bilirubin	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose.
	3-4	Permanently discontinue (see exception below)[1]	Permanently discontinue
Type 1 diabetes mellitus (if new onset) or Hyperglycemia	T1DM or 3-4	Hold pembrolizumab for new onset Type 1 diabetes mellitus or Grade 3-4 hyperglycemia associated with evidence of beta cell failure.	Resume pembrolizumab when patients are clinically and metabolically stable.
Hypophysitis	2-3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue
Hyperthyroidism	3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue
Hypothyroidism	2-4	Therapy with pembrolizumab can be continued while treatment for the thyroid disorder is instituted	Therapy with pembrolizumab can be continued while treatment for the thyroid disorder is instituted.
Infusion Reaction	3-4	Permanently discontinue	Permanently discontinue
Pneumonitis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	3-4	Permanently discontinue	Permanently discontinue
Renal Failure or Nephritis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	3-4	Permanently discontinue	Permanently discontinue
All Other Drug-Related Toxicity[2]	3 or Severe[3]	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue

Note: Permanently discontinue for any severe or Grade 3 drug-related AE that recurs or any life-threatening event.

[1] For patients with liver metastasis who begin treatment with Grade 2 AST or ALT, if AST or ALT increases by greater than or equal to 50% relative to baseline and lasts for at least 1 week then patients should be discontinued.

[2] Patients with intolerable or persistent Grade 2 drug-related AE may hold study medication at physician discretion. Permanently discontinue study drug for persistent Grade 2 adverse reactions for which treatment with study drug has been held, that do not recover to Grade 0-1 within 12 weeks of the last dose.

[3] Grade 3 drug-related amylase or lipase abnormality that is not associated with symptoms or clinical manifestations of pancreatitis

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Discontinue Subject
does not require dose delay.			

Dosing interruptions are permitted in the case of medical / surgical events or logistical reasons not related to study therapy (e.g., elective surgery, unrelated medical events, patient vacation, and/or holidays). Subjects should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the Sponsor. The reason for interruption should be documented in the patient's study record.

5.2.2 *Timing of Dose Administration*

Trial treatment should be administered on Day 1 of each cycle after all procedures/assessments have been completed as detailed on the Trial Flow Chart (Section 6.0). There is a ±7 day treatment window for Day 1 of each cycle.

All trial treatments will be administered on an outpatient basis.

Pembrolizumab 200 mg will be administered as a 30 minute IV infusion every 3 weeks. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min).

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

Vorinostat should be taken with food, at regular intervals regardless of pembrolizumab infusion time. On days the pt receives pembrolizumab, the vorinostat should be taken prior to the pembrolizumab infusion.

5.2.3 *Trial Blinding/Masking*

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

5.3 Randomization or Treatment Allocation

Patients who are enrolled on the phase II portion of the study and successfully complete the screening exams for initial registration will be randomized into one of two study arms. The study Biostatistician will generate a Flow Chart for Randomization. This Flow Chart will be held in confidence by the Biostatistician and the Clinical Trials Coordinator. The individual randomization assignment will be released by the Clinical Trials Coordinator only after the patient signs the informed consent document and successfully completes the screening process.

Treatment of patients on <u>Arm A</u>: Those patients randomized to Arm A will receive pembrolizumab alone.

Treatment of patients on Arm B: Those patients randomized to Arm B will receive pembrolizumab plus vorinostat.

5.4 Stratification

The patients will be stratified by histology and PD-L1 status, including the following three levels of PD-L1 membranous expression on tumor cells that have been scientifically justified: 1) Proportion Score (PS)1-49%, and PS≥50%.

5.5 Concomitant Medications/Vaccinations (allowed & prohibited)

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

5.5.1 *Acceptable Concomitant Medications*

All treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded in the source documentation 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 source documentation. Only those concomitant medications which are considered immunosuppressive such as steroids will be recorded in 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 as defined in Section 7.2 and ECIs as per the ECI guidance document.

5.5.2 *Prohibited Concomitant Medications*

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

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab
- Radiation therapy

  - Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed at the investigator's discretion.

- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine.

- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology or to treat a comorbid condition as a standard of care (e.g. COPD exacerbation). The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.
- HDAC inhibitors other than vorinostat.

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

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

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

5.6 Rescue Medications & Supportive Care

5.6.1 *Supportive Care Guidelines*

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

Note: if after the evaluation the event is determined not to be related, the investigator is instructed to follow the ECI reporting guidance but does not need to follow the treatment guidance (as outlined in the ECI guidance document). Refer to Section 5.2.1 for dose modification.

It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event. Suggested conditional procedures, as appropriate, can be found in the ECI guidance document.

- **Pneumonitis**:

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

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

  - All subjects who experience diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion. For Grade 2 or higher diarrhea, consider GI consultation and endoscopy to confirm or rule out colitis.
  - For **Grade 2 diarrhea/colitis** that persists greater than 3 days, administer oral corticosteroids.
  - For **Grade 3 or 4 diarrhea/colitis** that persists > 1 week, treat with intravenous steroids followed by high dose oral steroids.
  - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

- **Type 1 diabetes mellitus (if new onset, including diabetic ketoacidosis [DKA]) or ≥ Grade 3 Hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis (DKA)**

  - For **T1DM** or **Grade 3-4** Hyperglycemia
    - Insulin replacement therapy is recommended for Type I diabetes mellitus and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria.
    - Evaluate patients with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.

- **Hypophysitis**:

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

taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

- **Hyperthyroidism or Hypothyroidism**:
  Thyroid disorders can occur at any time during treatment. Monitor patients for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders.
  - **Grade 2** hyperthyroidism events (and **Grade 2-4** hypothyroidism):
    - In hyperthyroidism, non-selective beta-blockers (e.g. propranolol) are suggested as initial therapy.
    - In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyroinine, is indicated per standard of care.
  - **Grade 3-4** hyperthyroidism
    - Treat with an initial dose of IV corticosteroid followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

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

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

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

Table 8 below shows treatment guidelines for subjects who experience an infusion reaction associated with administration of pembrolizumab (MK-3475).

Table 8. Infusion Reaction Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for < =24 hrs	**Stop Infusion and monitor symptoms.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. **Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.**	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab (MK-3475) with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic).
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **Subject is permanently discontinued from further trial treatment administration.**	No subsequent dosing
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.		

5.7 Diet/Activity/Other Considerations

5.7.1 *Diet*

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

5.7.2 *Contraception*

Pembrolizumab may have adverse effects on a fetus in utero. Furthermore, it is not known if pembrolizumab has transient adverse effects on the composition of sperm. 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. Male subjects should agree to use an adequate method of barrier contraception starting with the first dose of study therapy through 120 days after the last dose of study therapy.

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

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study 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 Sponsor and to Merck. If there is any question that a subject will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

5.7.3 *Use in Pregnancy*

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

The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor. If a male subject impregnates his female partner the study personnel at the site must be informed

immediately and the pregnancy reported to the Sponsor and to Merck and followed as described above and in Section 7.2.2.

5.7.4 *Use in Nursing Women*

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

5.8 Subject Withdrawal/Discontinuation Criteria

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

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

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

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

  Note: *A subject may be granted an exception to continue on treatment with confirmed radiographic progression if clinically stable or clinically improved, please see Section 7.1.2.7.1*
- Unacceptable adverse experiences as described in Section 5.2.1.2
- Intercurrent illness that prevents further administration of treatment
- Investigator's decision to withdraw the subject
- Confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements
- Subject is lost to follow-up
- Completed 24 months of uninterrupted treatment with pembrolizumab or 35 administrations of study medication, whichever is later.

  Note: 24 months of study medication is calculated from the date of first dose. Subjects who stop pembrolizumab after 24 months may be eligible for up to one year of additional study treatment if they progress after stopping study treatment provided they meet the requirements detailed in Section 7.1.7.3.

- Administrative reasons

- A second episode of grade ≥ 2 pneumonitis mandates discontinuation of study therapy.

The End of Treatment and Follow-up visit procedures are listed in Section 6 (Protocol Flow Chart) and Section 7.1.5 (Visit Requirements). After the last dose of study drug, each subject will be followed for 30 days for adverse event monitoring (serious adverse events will be collected for 90 days after the end of treatment as described in Section 7.2.3.1). Subjects who discontinue for reasons other than progressive disease will have post-treatment follow-up for disease status until disease progression, initiating a non-study cancer treatment, withdrawing consent or becoming lost to follow-up. After documented disease progression each subject will be followed by telephone for overall survival until death, withdrawal of consent, or the end of the study, whichever occurs first.

5.8.1 *Discontinuation of Study Therapy after CR*

Discontinuation of treatment may be considered for subjects who have attained a confirmed CR that have been treated for at least 24 weeks with pembrolizumab and had at least two treatments with pembrolizumab beyond the date when the initial CR was declared. Subjects who then experience radiographic disease progression may be eligible for up to one year of additional treatment with pembrolizumab via the Second Course Phase at the discretion of the investigator if no cancer treatment was administered since the last dose of pembrolizumab, the subject meets the safety parameters listed in the Inclusion/Exclusion criteria, and the trial is open. Subjects will resume therapy at the same dose and schedule at the time of initial discontinuation. Additional details are provided in Section 7.1.7.3.

5.9 Subject Replacement Strategy

5.10 Clinical Criteria for Early Trial Termination

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

1. Quality or quantity of data recording is inaccurate or incomplete

2. Poor adherence to protocol and regulatory requirements

3. Incidence or severity of adverse drug reaction in this or other studies indicates a potential health hazard to subjects

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

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

6.0 TRIAL FLOW CHART

6.1 Study Flow Chart*

Trial Period:	**Treatment Cycles**									**End of Treatment**	**Post-Treatment**		
Treatment Cycle/Title:	Study Screening (Visit 1)	1	2	3	4	To be repeated beyond 8 cycles				Discon	Safety Follow-up	Follow Up Visits	Survival Follow-Up
						5	6	7	8				
Scheduling Window (Days):	-27 to c1d1[e]		± 7	± 7	± 7	± 7	± 7	± 7	± 7	At time of Discon	30 days post last dose of study drug	Every 8 weeks post discon	Every 12 weeks
Screening Consent	X												
Informed Consent	X												
Inclusion/Exclusion Criteria	X												
Demographics and Medical History	X												
Prior and Concomitant Medication Review	X	X	X	X	X	X	X	X	X				
Vorinostat compliance review/Pill Diary		X	X	X	X	X	X	X	X	X			
Trial Treatment Administration		X	X	X	X	X	X	X	X				
Post-study anticancer therapy status										X	X		X
Survival Status		X	X	X	X	X	X	X	X	X			X
Review Adverse Events	X[f]	X	X	X	X	X	X	X	X	X	X		
Full Physical Examination	X												
Directed Physical Examination		X	X	X	X	X	X	X	X	X	X		
Vital Signs and Weight	X	X	X	X	X	X	X	X	X	X	X		
ECOG Performance Status	X	X	X	X	X	X	X	X	X		X		
Pregnancy Test – Urine or Serum b-HCG	X	X	X	X	X	X	X	X	X		X		

Trial Period:	**Treatment Cycles**									**End of Treatment**	**Post-Treatment**		
Treatment Cycle/Title:	Study Screening (Visit 1)	1	2	3	4	To be repeated beyond 8 cycles 5	6	7	8	Discon	Safety Follow-up	Follow Up Visits	Survival Follow-Up
Scheduling Window (Days):	-27 to c1d1[e]		± 7	± 7	± 7	± 7	± 7	± 7	± 7	At time of Discon	30 days post last dose of study drug	Every 8 weeks post discon	Every 12 weeks
PT/INR and aPTT	X	X (C1D15 -C1D21											
CBC with Differential	X	X	X	X	X	X	X	X	X		X		
Comprehensive Serum Chemistry Panel	X	X	X	X	X	X	X	X	X	X	X		
Magnesium	X	X	X	X	X	X	X	X	X	X	X		
Urinalysis	X												
T3, FT4 and TSH	X	X	X	X	X	X	X	X	X	X	X		
Echocardiogram [g]	X												
EKG	X												
Tumor Imaging (CT Thorax/Abdomen)	X			X		X		X		X		X[d]	
Brain MRI or Brain CT	X												
Archival or Newly Obtained Tissue Collection[a,b]	X	X (C1D15 -C1D21											
Correlative Studies Blood Collection[c]	X[c]	X[c]		X		X		X		X		X	

Trial Period:	**Treatment Cycles**									**End of Treatment**	**Post-Treatment**		
						To be repeated beyond 8 cycles							
Treatment Cycle/Title:	Study Screening (Visit 1)	1	2	3	4	5	6	7	8	Discon	Safety Follow-up	Follow Up Visits	Survival Follow-Up
Scheduling Window (Days):	-27 to c1d1[e]		± 7	± 7	± 7	± 7	± 7	± 7	± 7	At time of Discon	30 days post last dose of study drug	Every 8 weeks post discon	Every 12 weeks

*All clinic visits and tests (including labs, imaging studies and biopsies) will have a plus or minus 7 day window for completion.

[a] All patients in the study are required to have a pre-treatment biopsy, where feasible, or archival tissue from after the most recent line of therapy, which will be tested for PD-L1 and nanostring analyses.

[b] C1D15-21 biopsies will be done on patients in the phase I dose escalation, phase Ib and phase II parts of the study, where feasible. PD-L1 and Nanostring studies will be completed on all of these biopsy specimens.

[c] Timepoints for the first two correlative study blood collection include first during Screening or on C1D1, and second on C1D15. The remainder of the blood collections will occur with the reimaging scans. Histone acetylation studies will be run on serial PBMC draws in all patients (includes phase I dose escalation, phase Ib expansion and phase II). The blood will be collected in five 10 mL green top (sodium heparin) tubes for a total of about 50mL of whole blood.

[d] Subjects who discontinue trial treatment for a reason other than disease progression will move into the Follow-Up Phase and should be assessed every 8 weeks (56 ± 7 days) by radiologic imaging to monitor disease status. After 1 year, the imaging time point will occur every 12 weeks (± 7 days).

[e] The main study screening window will occur within 28 days prior to the first study treatment. Note additionally that screening laboratory blood and urine studies must be obtained within 10 days of C1D1, with the exception of pregnancy testing in applicable patients, which must be obtained within 72 hours of first treatment.

[f] Only serious adverse events will be collected during the screening window.

[g] Echocardiogram will be performed at screening for baseline, and may be repeated if clinically indicated per the treating investigator. Echocardiogram should be performed within 30 days of treatment initiation.

7.0 TRIAL PROCEDURES

7.1 Trial Procedures

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

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

7.1.1 *Administrative Procedures*

7.1.1.1 Informed consent

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

7.1.1.1.1 General Informed Consent

Consent must be documented by the subject's dated signature or by the subject's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

The investigator is responsible for patient care and for obtaining consent by the patient. Written informed consent must be obtained prior to entry of any patient. The informed consent will adhere to IRB requirements, applicable laws and regulations and Sponsor requirements.

7.1.1.2 Inclusion/Exclusion Criteria

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

7.1.1.3 Medical History

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

7.1.1.4 Prior and Concomitant Medications Review

7.1.1.4.1 Prior Medications

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

7.1.1.4.2 Concomitant Medications

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

7.1.1.5 Disease Details and Treatments

7.1.1.5.1 Disease Details

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

7.1.1.5.2 Prior Treatment Details

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

7.1.2 *Assignment of Screening Number*

Once a patient is enrolled in the study, he/she will be assigned a simple 3 digit number, with the first patient assigned to 001 and so on. A separate spreadsheet with password protection will be maintained that contains the patient study number along with personally identifiable information. Password protection will be maintained in order to keep patient information strictly confidential. Upon signing the informed consent form, the patient will be assigned a subject number by the investigator or his/her designee. Once assigned to a patient, a subject number will not be reused. If the patient fails to be started on treatment for any reason, the reason will be entered on the Eligibility Tab in OnCore, and his/her demographic information will be entered on the Demography Tab in OnCore. All laboratory, radiologic, and pathologic data collected on trial participants will be assigned the unique treatment number and stored in the OnCore system database.

7.1.3 *Assignment of Randomization Number*

Patients who successfully complete the screening exams for initial registration will be randomized into one of two study arms. Randomization will be accomplished using the Moffitt Cancer Center web-based Subject Registration and Randomization System (SRAR). The SRAR program is accessed using an individual secure identification key that authenticates the user into the Moffitt network

The study Biostatistician will generate a Flow Chart for Randomization. This Flow Chart will be held in confidence by the Biostatistician and the Clinical Trials Coordinator. The individual randomization assignment will be released by the Clinical Trials Coordinator only after the patient signs the informed consent document and successfully completes the screening process.

Treatment of patients on Arm A: Those patients randomized to Arm A will receive pembrolizumab alone.

Treatment of patients on Arm B: Those patients randomized to Arm B will receive pembrolizumab plus vorinostat.

7.1.3.1 Trial compliance (medication/diet/activity/other)

The Principal Investigator and the Clinical Research Coordinator assigned to the case will be primarily responsible for maintaining all study related documents including the clinical research forms. Oncore is the password protected, web-based electronic secure, database of record for all CRF entries and will be verified with source documentation. The review of medical records within the EMR will be done in a manner to assure that patient confidentiality is maintained. Vorinostat compliance review will take place via a medication diary review as indicated in the study calendar.

7.1.4 *Clinical Procedures/Assessments*

7.1.4.1 Adverse event (AE) monitoring

AEs will be collected from time of C1D1. 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 11.2). Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

For subjects receiving treatment with pembrolizumab all AEs of unknown etiology associated with pembrolizumab exposure should be evaluated to determine if it is possibly an event of clinical interest (ECI) of a potentially immunologic etiology (termed immune-related adverse events, or irAEs); see the separate ECI guidance document in Appendix 4 regarding the identification, evaluation and management of potential irAEs.

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

7.1.4.2 Full physical exam

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

7.1.4.3 Directed physical exam

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

7.1.4.4 Vital signs

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

7.1.4.5 Eastern Cooperative Oncology Group (ECOG) Performance Scale

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

7.1.4.6 Tumor imaging and assessment of disease

Patients will undergo a CT Thorax and Abdomen at baseline, then every 2 cycles. After 1 year of follow-up, the interval of CT will be extended to once every 12 weeks. Radiographic assessments will be based on Response Evaluation Criteria in Solid Tumors v1.1 (RECIST v1.1). Subjects with progressive disease by RECIST v1.1 but without rapid clinical deterioration may continue to be treated at the discretion of the investigator.

Baseline Brain MRI or Brain CT will be required.

7.1.4.7 Tumor tissue collection and correlative studies blood sampling

See section 4.2.

7.1.5 *Laboratory Procedures/Assessments*

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

Laboratory tests for hematology, chemistry, urinalysis, and others are specified in **Table 9**.

Table 9. Laboratory Tests

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

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

‡ If considered standard of care in your region.

Laboratory tests for screening or entry into the Second Course Phase should be performed within 10 days prior to the first dose of treatment. Any screening labs done within 7 days of C1D1 do not need to be repeated prior to first treatment. After Cycle 1, pre-dose laboratory procedures can be conducted up to 72 hours prior to dosing. Results must be reviewed by the investigator or qualified designee and found to be acceptable prior to each dose of trial treatment.

7.1.5.2 Pharmacodynamic evaluations

See section 4.3.3.1.

Blood Collection for Anti-Pembrolizumab Antibodies

7.1.6 *Other Procedures*

7.1.6.1 Withdrawal/discontinuation

When a subject discontinues/withdraws prior to trial completion, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.2 - Assessing and Recording Adverse Events. Subjects who a) attain a CR or b) complete 24 months of treatment with pembrolizumab may discontinue treatment with the option of restarting treatment if they meet the criteria specified in Section 7.1.7.3. After discontinuing treatment following assessment of CR, these subjects should return to the site for a Safety Follow-up Visit (described in Section 7.1.5.3.1) and then proceed to the Follow-Up Period of the study (described in Section 7.1.5.4).

7.1.7 *Visit Requirements*

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

7.1.7.1 Safety follow-up visit

The mandatory Safety Follow-Up Visit should be conducted approximately 30 days after the last dose of trial drug administration or before the initiation of a new anti-cancer treatment, whichever comes first. All AEs that occur prior to the Safety Follow-Up Visit should be recorded. Subjects with an AE of Grade > 1 will be followed until the resolution of the AE to Grade 0-1 or until the beginning of a new anti-neoplastic therapy, whichever occurs first. SAEs that occur within 90 days of the end of treatment or before initiation of a new anti-cancer treatment should also be followed and recorded. Subjects who are eligible for retreatment with pembrolizumab (as described in Section 7.1.7.3) may have up to two safety follow-up visits, one after the Treatment Period and one after the Second Course Phase.

7.1.7.2 Follow-up visits

Subjects who discontinue trial treatment for a reason other than disease progression will move into the Follow-Up Phase and should be assessed every 8 weeks (56 ± 7 days) by radiologic imaging to monitor disease status. After 1 year, the imaging time point will occur

every 12 weeks (± 7 days). Every effort should be made to collect information regarding disease status until the start of new anti-neoplastic therapy, disease progression, death, end of the study or if the subject begins retreatment with pembrolizumab as detailed in Section 7.1.7.3. Information regarding post-study anti-neoplastic treatment will be collected if new treatment is initiated.

Subjects who are eligible to receive retreatment with pembrolizumab according to the criteria in Section 7.1.7.3 will move from the follow-up phase to the Second Course Phase when they experience disease progression.

7.1.7.2.1 Survival Follow-up

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

7.1.7.3 Second course phase (retreatment period)

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

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

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

AND

- Experienced an investigator-determined confirmed radiographic disease progression after stopping their initial treatment with pembrolizumab
- Did not receive any anti-cancer treatment since the last dose of pembrolizumab
- Has a performance status of 0 or 1 on the ECOG Performance Scale
- Demonstrates adequate organ function as detailed in Section 5.1.2

- Female subject of childbearing potential should have a negative serum or urine pregnancy test within 72 hours prior to receiving retreatment with study medication.

- Female subject of childbearing potential should be willing to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of study medication (Reference Section 5.7.2). Subjects of child bearing potential are those who have not been surgically sterilized or have been free from menses for > 1 year.

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

- Does not have a history or current evidence of any condition, therapy, or laboratory abnormality that might interfere with the subject's participation for the full duration of the trial or is not in the best interest of the subject to participate, in the opinion of the treating investigator.

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

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

7.2 Assessing and Recording Adverse Events

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the Merck's product, is also an adverse event. The start of AE collections will be C1D1. Abnormal Lab values, vital signs or test results that do not induce clinical signs/symptoms or require therapy, will not be considered clinically significant and will not be reported as Adverse Events.

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

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

Adverse events may occur during the course of the use of Merck product in clinical trials or within the follow-up period specified by the protocol, or prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal.

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

Progression of the cancer under study is not considered an adverse event unless it is considered to be drug related by the investigator.

All adverse events will be recorded from C1D1 through 30 days following cessation of treatment and at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in section 7.2.3.1.

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

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

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

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

All reports of overdose with and without an adverse event must be reported within 24 hours to the Sponsor and within 2 working days hours to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220)

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

Although pregnancy and lactation are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy 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 24 hours to the Sponsor and within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220)

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

7.2.3.1 Serious adverse events

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

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

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

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 facsimile number: +1-215-993-1220

A copy of all 15 Day Reports and Annual Progress Reports is submitted as required by FDA, European Union (EU), Pharmaceutical and Medical Devices agency (PMDA) or other local regulators. Investigators will cross reference this submission according to local regulations to the Merck Investigational Compound Number (IND, CSA, etc.) at the time of submission.

Additionally investigators will submit a copy of these reports to Merck & Co., Inc. (Attn: Worldwide Product Safety; FAX 215 993-1220) at the time of submission to FDA.

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

7.2.3.2 Events of clinical interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be recorded as such on the Adverse Event case report forms/worksheets and reported **within 24 hours** to the Sponsor and **within 2 working days** to Merck Global Safety (Attn: Worldwide Product Safety; FAX 215 993-1220). Events of clinical interest for this trial include:

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

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

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

3. Additional adverse events:

   A separate guidance document has been provided entitled “Event of Clinical Interest Guidance Document” (previously entitled, “Event of Clinical Interest and Immune-Related Adverse Event Guidance Document”). This document can be found in Appendix 4 and provides guidance regarding identification, evaluation and management of ECIs and irAEs.

   ECIs (both non-serious and serious adverse events) identified in this guidance document from the date of first dose through 30 days following cessation of treatment, need to be reported **within 24 hours** to the Sponsor and **within 2 working days** to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220), regardless of attribution to study treatment, consistent with standard SAE reporting guidelines.

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

7.2.4 *Evaluating Adverse Events*

An investigator who is a qualified physician will evaluate all adverse events according to the NCI Common Terminology Criteria 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 10. Evaluating Adverse Events

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

V4.0 CTCAE Grading	**Grade 1**	**Mild; asymptomatic or mid symptoms; clinical or diagnostic observations only; intervention not indicated.**
	Grade 2	**Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.**
	Grade 3	**Severe or medically significant but not immediately life-threatening; hospitalization or prolongation or hospitalization indicated; disabling; limiting self-care ADL.**
	Grade 4	**Life threatening consequences; urgent intervention indicated.**
	Grade 5	**Death related to AE**
Seriousness	A serious adverse event is any adverse event occurring at any dose or during any use of Merck product that:	
	†**Results in death**; or	
	†**Is life threatening; or** places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred (Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.); or	
	†**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or	
	†**Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization [including hospitalization for an elective procedure] for a preexisting condition which has not worsened does not constitute a serious adverse event.); or	
	†**Is a congenital anomaly/birth defect** (in offspring of subject taking the product regardless of time to diagnosis);or	
	Is a new **cancer;** (that is not a condition of the study) **or**	
	Is an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported within 24 hours.	
	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	
Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units	
Action taken	Did the adverse event cause the Merck product to be discontinued?	
Relationship to test drug	Did the Merck product cause the adverse event? The determination of the likelihood that the Merck product caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test drug and the adverse event based upon the available information. **The following components are to be used to assess the relationship between the Merck product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Merck product caused the adverse event (AE):	
	Exposure	Is there evidence that the subject was actually exposed to the Merck product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
	Time Course	Did the AE follow in a reasonable temporal sequence from administration of the Merck product? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?
	Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors

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

7.2.5 *Sponsor Responsibility for Reporting Adverse Events*

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

8.0 STATISTICAL ANALYSIS PLAN

8.1 Statistical Analysis Plan Summary

The phase I dose escalation will utilize the modified continuous reassessment method (mCRM) to identify the MTD. A "pick-the-winner" design for the randomized phase II clinical trial is proposed by employing Simon minimax two-stage design and Bayesian posterior probability. This design will have an 86% overall power to claim arm B as the winner when the true probabilities of response with arms A and B are 18% and 38%, respectively. The power slightly deceases to 75% when the response rate is 23% in arm A with 38% in arm B. The power is 57% when there is only 10% difference of response rate (arm A: 28%; arm B: 38%). The type I error is controlled at 16%.

8.2 Statistical Analysis Plan

8.2.1 *Phase I dose escalation.*

The primary objective of this phase I dose escalation is to find a maximum tolerated dose (MTD) corresponding to a risk of DLT occurring in 30% of patients. Two dose levels have been identified for experimentation (200mg PO daily and 400mg PO daily) with a back-up dose at 100mg PO daily, and due to safety concerns the first cohort of patients will receive the lowest dose (200mg). The study uses the modified continuous reassessment method (mCRM) described later to design dose escalation (O'Quigley et al., 1990). The design will recruit patients in cohorts of three patients each and will not allow for dose-skipping during escalation. A total of 12 patients will be enrolled for the Phase I dose escalation. The initial guess of the risk of DLT at the lowest dose (200mg) is 10% whilst the best guess of the MTD is at dose level 2 (400mg) (i.e., a 30% risk of DLT at this dose level). The initial guesses of risk of DLT are established for each dose level as shown in Table 10.

Table 10. Initial estimates of the probability of DLT at each dose level.

	Dose cohort		
	100mg PO Daily (back-up dose)	200mg PO Daily (starting dose)	400mg PO Daily
initial guessed DLT probability	1%	10%	30%

8.2.2 *Definitions for Dose Limiting Toxicities.*

The period for evaluating DLTs is defined as the time period starting with the first dose of investigational products until the planned administration of the second dose of pembrolizumab. Subjects are considered evaluable for assessment of DLTs if they receive at least 75% of the protocol assigned doses of both pembrolizumab and vorinostat and complete the safety follow-up through the end of the DLT evaluation period, or experience a DLT during the DLT evaluation period.

Subjects who do not remain on the study up to this time for reasons other than DLT will be replaced with another subject at the same dose level. DLTs will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE v4.03). A DLT will be defined as any Grade 3 or higher toxicity that occurs during the DLT evaluation period. Toxicity that is clearly and directly related to the primary disease or to another etiology is excluded from this definition.

The following will be DLTs:

- Any Grade 4 immune-related adverse event (irAE)
- Any ≥ Grade 3 colitis
- Any Grade 3 or 4 non-infectious pneumonitis irrespective of duration
- Any Grade 2 pneumonitis that does not resolve to ≤ Grade 1 within 3 days of the initiation of maximal supportive care
- Any Grade 3 irAE, excluding colitis or pneumonitis, that does not downgrade to Grade 2 within 3 days after onset of the event despite optimal medical management including systemic corticosteroids or does not downgrade to ≤ Grade 1 or baseline within 14 days
- Liver transaminase elevation > 8 × upper limit of normal (ULN) or total bilirubin > 5 × ULN
- Any ≥ Grade 3 non-irAE, except for the exclusions listed below

The definition excludes the following conditions:

- Grade 3 fatigue lasting ≤ 7 days
- Grade 3 endocrine disorder (thyroid, pituitary, and/or adrenal insufficiency) that is managed with or without systemic corticosteroid therapy and/or hormone replacement therapy and the subject is asymptomatic
- Grade 3 inflammatory reaction attributed to a local antitumor response (eg, inflammatory reaction at sites of metastatic disease/lymph nodes)
- Concurrent vitiligo or alopecia of any AE grade
- Grade 3 infusion-related reaction (first occurrence and in the absence of steroid prophylaxis) that resolves within 6 hours with appropriate clinical management
- Grade 3 or 4 neutropenia that is not associated with fever or systemic infection that improves by at least 1 grade within 3 days. Grade 3 or Grade 4 febrile neutropenia will be a DLT regardless of duration or reversibility
- Grade 3 or 4 lymphopenia
- Grade 3 thrombocytopenia that is not associated with clinically significant bleeding that requires medical intervention, and improves by at least 1 grade within 3 days

- Isolated Grade 3 electrolyte abnormalities that are not associated with clinical signs or symptoms and are reversed with appropriate maximal medical intervention within 3 days
- Grade 3 amylase or lipase abnormality that is not associated with symptoms or clinical manifestations of pancreatitis
- Immune-related AEs are defined as AEs of an immune nature (ie, inflammatory) in the absence of a clear alternative etiology. In the absence of a clinically significant abnormality, repeat laboratory testing will be conducted to confirm significant laboratory findings prior to designation as a DLT. Laboratory abnormalities that are not deemed to be clinical significant will not be considered a DLT.

While the rules for adjudicating DLTs in the context of dose exploration are specified above, an AE not listed above may be defined as a DLT after a consultation with the sponsor and investigators, based on the emerging safety profile.

8.2.3 *Dose escalation.*

The maximum tolerated dose (MTD) is defined as the dose with the DLT rate of 30%.
Starting at the first dose level of 200mg PO daily, if there are < 1 DLT then it is acceptable to escalate to the next dose level. If no DLT is observed at the first dose level (200mg PO daily) with 3 subjects, then dose escalation will continue with dosing groups of 3 subjects at a time. This will continue up to dose level 2 (400mg of vorinostat). The DLT assessment period is the first 21 days of treatment.

If a DLT is observed at 200 mg PO daily, then the vorinostat dose will be de-escalated to 100 mg PO daily with the intent of increasing the dose back to 200 mg PO daily if 100 mg PO daily is shown to be safe and well-tolerated. After the first DLT is observed or any proposed dose level is achieved without any DLTs, subsequent dose assignments are guided by the modified continuous reassessment method (mCRM) as described below.

The mCRM works in the following way. If n subjects have been assigned and completed 21 days of follow-up, let Yi=1 if the i^{th} subject experienced DLT and let Yi=0 otherwise, for i = 1,…, n. The mCRM model (O'Quigley et al. 1990) used here is

$$\text{Prob}(Yi=1|\text{dose level k})=\boldsymbol{F}(\theta, \text{dose level k})= \exp(3+ \theta\times \text{dose}_{(k)}^*)/(1+ \exp(3+ \theta\times \text{dose}_{(k)}^*)$$

where θ is the parameter to be estimated for the model, ***F*** is the probability of a subject *i* experiencing a DLT at dose level *k*, the $\text{dose}_{(k)}^*$ is the standardized dose. The prior distribution on parameter *θ* is assumed to be a gamma distribution with shape=1 and scale=1. The Bayes' theorem is used to update the prior distribution of *θ*. After each subject's response is observed, the mean posterior density of the parameter, *θ,* is computed.

The dose to be administered to the next subject is the dose x_{n+1} such that |Prob(y=1| x_{n+1}, $\theta^{(n)}$) – 0.3| is minimized (i.e., the dose with the estimated DLT rate closest to the target rate of 0.3). When a dose is escalated, skipping dose levels is not allowed so that any escalation would only be to the next higher dose level in the predefined sequence. When a dose is de-escalated, a dose level can be skipped.

The total sample size of the dose escalation followed by the mCRM to obtain the estimate of the MTD is 12 subjects. After each dosing group, the mCRM will provide a current estimate of the MTD, which will be recommended as the next dose. The DMC will determine when these estimates of the MTD become consistent to declare the MTD.

Here is one hypothetical example (Table 11 and Figure 5) to illustrate how the mCRM works. Figure 6 summarizes the results of posterior probability of DLT in each dose and suggests the 400mg as the recommended dose (MTD).

1. Assign the first 3 patients to the dose 200mg. 0 DLT is observed. The estimated toxicity rate is 1.1% in dose 100mg, 4.6% in dose 200mg, 10.9% in dose 400mg. The dose cohorts, 400mg, have a toxicity rate closer to 30% compared to the one in dose 200mg. Since dose-skipping during escalation is not allowed, the dose 400mg is chosen for the next 3 patients.
2. Assign 4-6 patients to the dose 400mg. 1 DLT is observed. The estimated toxicity rate is 2% in dose 100mg, 10.3% in dose 200mg, 25.5% in dose 400mg. Dose cohort, 400mg, has a toxicity rate closest to the target toxicity rate (30%), so the dose 400mg is chosen for the next 3 patients by the mCRM algorithm.
3. Assign 7-9 patients to the dose 400mg. 1 DLT is observed. The estimated toxicity rate is 1.9% in dose 100mg, 11.4% in dose 200mg, 28.7% in dose 400mg. Dose cohort, 400mg, has a toxicity rate closest to the target toxicity rate (30%), so the dose 400mg is chosen for the next 3 patients by the mCRM algorithm.
4. Assign 10-12 patients to the dose 400mg. 1 DLT is observed. The estimated toxicity rate is 1.8% in dose 100mg, 11.7% in dose 200mg, 30.1% in dose 400mg. Dose cohort 400mg has a toxicity rate closest to the target toxicity rate (30%). And it reaches the maximum of the sample size (n=12). The mCRM algorithm claims the dose 400mg as MTD.

Table 11. Hypothetical example of the modified continuous reassessment method (mCRM).

Patient ID	Dose	DLT (DLT=1)		Level -1 (100mg)	Level 1 (200mg)	Level 2 (400mg)
1	200mg	0				
2	200mg	0				
3	200mg	0				
			Estimated toxicity rate at end of this	1.10%	4.60%	10.90%

			dose 200mg			
				Dose 400mg has the toxicity rate closest to the target toxicity rate (30%), so the dose 400mg is chosen for the next 3 patients.		
4	400mg	0				
5	400mg	0				
6	400mg	1				
			Estimated toxicity rate at end of this dose 400mg	2%	10.30%	25.50%
				Dose 400mg has the toxicity rate closest to the target toxicity rate (30%), so the dose 400mg is chosen for the next 3 patients.		
7	400mg	0				
8	400mg	1				
9	400mg	0				
			Estimated toxicity rate at end of this dose 400mg	1.90%	11.40%	28.70%
				Dose 400mg has the toxicity rate closest to the target toxicity rate (30%), so the dose 400mg is chosen for the next 3 patients.		
10	400mg	0				
11	400mg	0				
12	400mg	1				
			Estimated toxicity rate at end of this dose 400mg	1.80%	11.70%	30.10%
				The mCRM algorithm claims the dose 400mg as MTD.		

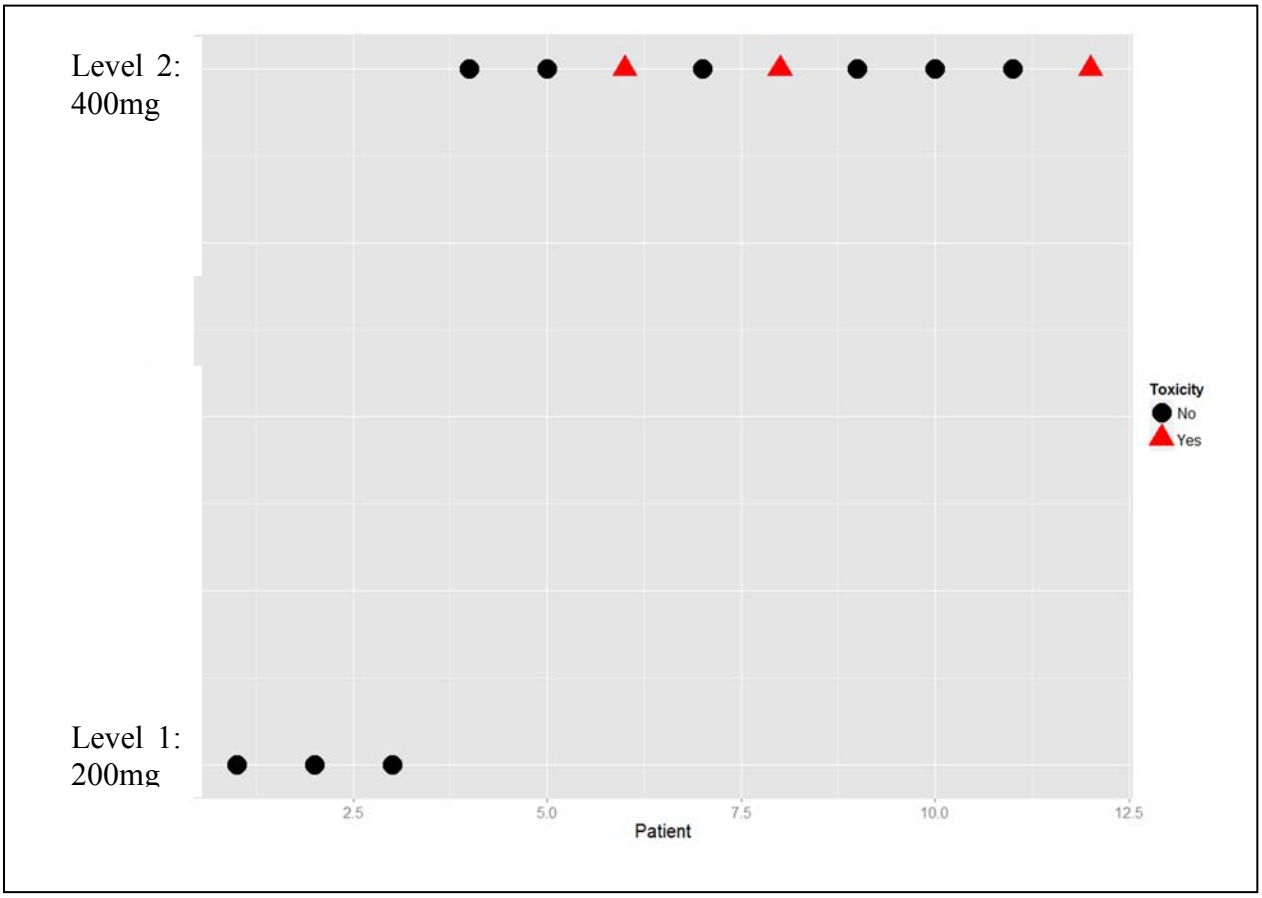

Level 2: 400mg
Level 1: 200mg
Toxicity
No
Yes
2.5
5.0
7.5
10.0
12.5
Patient

Figure 5. Hypothetical example of the modified continuous reassessment method (mCRM).

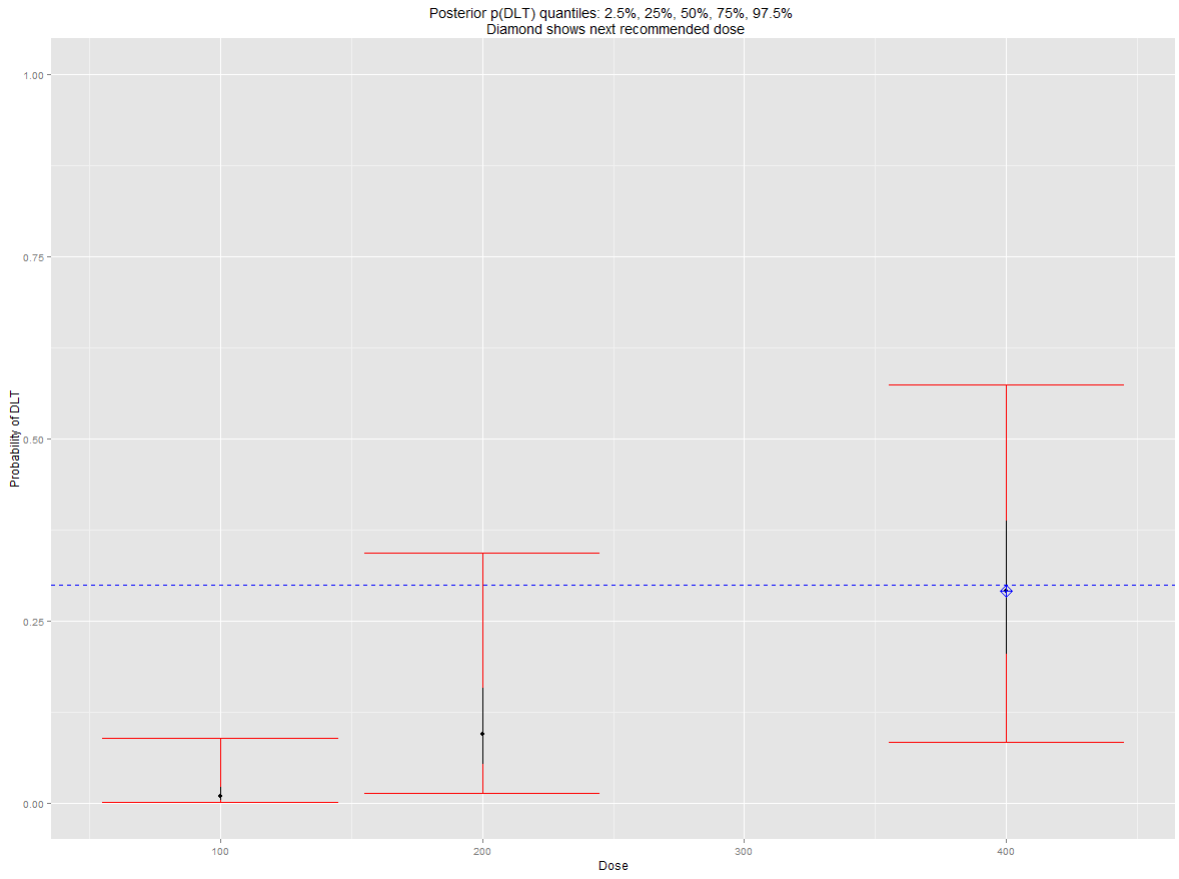


Figure 6. A summary of the results of posterior probability of DLT at each dose level. The model suggests the 400mg as the recommended dose (MTD) depicted by the diamond.

8.2.4 *Operating characteristics.*

Table 12 shows a simulation study conducted to illustrate the performance of the design in various conditions. Specifically, we explored different scenarios from toxicity as expected and greater than expected. Our initial guess of DLT probability is 1% for 100mg dose, 10%

for 200mg dose, and 30% for 400mg dose). Scenario 1 is the case that our initial guessed of DLT probability is same as the true DLT probability. Scenario 2 and 3 are the case that the true DLT probability is greater than our initial guessed of DLT probability with 100mg and 200 mg as MTD, respectively. Scenario 4 is the same as Scenario 1 except a higher DLT probability in the back-up dose.

Table 12. A simulation study to depict the mCRM design for various conditions. The MTD is highlighted in each scenario.

	100mg (back-up dose)	200mg (starting dose)	400mg
Prior guess of DLT probability	**1%**	**10%**	**30%**
Scenario 1 (Toxicity as expected)	1%	10%	30%
Scenario 2 (greater than expected: 100mg as MTD)	30%	40%	60%
Scenario 3 (greater than expected: 200mg as MTD)	10%	30%	50%
Scenario 4 (greater than expected: 400mg as MTD)	5%	10%	30%

Simulation results show that in each of these scenarios, the mCRM study design with 12 subjects is superior to the 3+3 design in estimating the MTD correctly. Table 13 reports the probability of a dose to be selected as MTD (Percent Recommendation) and the probability of patients assigned to each dose level (Percent Experimentation). Ideally, if the mCRM design works well, we expect it will choose the true MTD dose with the highest probability (i.e., highest Percent Recommendation) and assign more patients in the true MTD dose (i.e., highest Percent Experimentation).

In Scenario 1 with 400mg as true MTD, the mCRM design yields a high probability of 83.3% to claim 400mg as MTD. In contrast, the 3+3 design results in 44.8% to claim 400mg as

MTD and 44.8% for 200mg as MTD. Regarding probability of patients assigned to each dose level, ideally we would like to see more patients assigned in the MTD dose. There are 56.7% patients assigned to the 400mg by the mCRM design compared to 42.7% by the 3+3 design.

In Scenario 2 with 100mg as true MTD, the probability to claim 100mg as MTD is 54.5% by the mCRM design and 20.4% by the 3+3 design. There are 34.3% patients assigned to the 100mg by the mCRM design compared to 40.3% by the 3+3 design.

In Scenario 3 with 200mg as true MTD, the probability of 200mg as MTD is 53.2% by mCRM design and 34.8% by 3+3 design. There are 58.2% patients assigned to the 200mg by the mCRM design compared to 49.4% by the 3+3 design.

In Scenario 4 with 400mg as true MTD, the probability of 400mg as MTD is 83.5% by the mCRM design and 44.8% by the 3+3 design. Both designs have 42.7%-57.3% patients assigned to the 400mg dose level (mCRM: 57.3%; 3+3 design: 42.7%).

These simulations show that the proposed mCRM design with 12 subjects is superior to the 3+3 design in that it has a higher probability of estimating the MTD correctly.

Table 13. The mCRM would allow more patients to be exposed to the MTD as compared to the 3+3 design. The simulation scenarios are associated with a probability of a dose to be selected as the MTD (Percent Recommendation) and a proportion of patients assigned to each dose level (Percent Experimentation).

		Probability of a dose to be selected as MTD (Percent Recommendation)					Probability of patients assigned to each dose level (Percent Experimentation)		
		Dose Cohort					Dose Cohort		
	Method	<100mg	100mg	200mg	400mg		100mg	200mg	400mg
Scenario 1 (Toxicity as expected: 400mg as true MTD)	CRM (n=12)	0.0%	0.4%	16.3%	83.3%		1.6%	41.7%	56.7%
	3+3 (n=9.38)	0.3%	10.1%	44.8%	44.8%		5.5%	51.8%	42.7%
Scenario 2 (greater than expected: 100mg as true MTD)	CRM (n=12)	0.0%	54.5%	36.6%	8.9%		34.3%	53.4%	12.3%

	3+3 (n=10.16)	55.7 %	20.4 %	21.4 %	2.5%		40.3%	48.5%	11.2%
Scenario 3 (greater than expected: 200mg as true MTD)	CRM (n=12)	0.0%	21.7 %	53.2 %	25.1 %		18.6%	58.2%	23.3%
	3+3 (n=10.57)	16.5 %	40.2 %	34.8 %	8.5%		30.9%	49.4%	19.7%
Scenario 4 (greater than expected: 400mg as true MTD)	CRM (n=12)	0.0%	1.0%	15.5 %	83.5 %		1.8%	40.9%	57.3%
	3+3 (n=9.38)	1.5%	8.9%	44.8 %	44.8 %		5.5%	51.8%	42.7%

Randomized Phase II Statistical Design: Simon two-stage design + Bayesian posterior probability.

A "pick-the-winner" design for the randomized phase II clinical trial is proposed by employing Simon minimax two-stage design and Bayesian posterior probability(Chen et al., 2017). Specifically, a Simon minimax two-stage design will be used for each experimental arm (Simon, 1989). If both arms fail at the first or second stage, the trial will stop. No winner will be claimed. If only one arm pass the second stage, the arm will be the winner. If both arms pass the second stage, we will use a Bayesian posterior probability, $r_{B>A,}$ (probability of the response rate in arm B higher than in arm A) to select the winner. Table 14 lists the rule to claim a winner. The operating characteristics of this design are detailed in the sample size calculation.

Table 14. Depiction of the Simon optimal two-stage or "pick-the-winner" design.

		Arm B		
		fail in stage 1	fail in stage 2	pass 2nd stage
Arm A	fail in stage 1	both losers	both losers	Arm B winner
	fail in stage 2	both losers	both losers	Arm B winner
	pass 2nd stage	Arm A winner	Arm A winner	Arm B winner if $r_{B>A} > 80\%$ Arm A winner if $r_{B>A} < 20\%$

$r_{B>A}$: posterior probability of the response rate in arm B higher than in arm A

This design has several features: (1) Randomization reduces selection bias and allows a greater degree of comparability, (2) the Simon two-stage design will allow for termination of an ineffective regimen earlier when compared to historical control data, and (3) the Bayesian posterior probability provides additional power to detect a definitive differential treatment effect. This trial design will allow us to more accurately determine if it is worthwhile to conduct a large phase III trial. We have used this trial design in a randomized three-arm phase II trial (p53 vaccine and ATRA) and were able to terminate two arms due to lack of efficacy and feasibility. This allowed us to focus on the arm with p53 vaccine plus ATRA for efficacy evaluation (Creelan et al., 2013).

8.2.5 *Descriptive statistics*

For each arm, summaries of the primary endpoint (response rate) and important descriptors (e.g., age, gender) will be produced using descriptive statistics such as mean and standard deviation for measured continuous variables and marginal distributions for categorical variables. We will also use histograms and box-plots to understand aspects of data quality and overall characteristics of the data. All patients enrolled in the study will be included in the analysis (intention-to-treat analysis). No adjustments to the data are intended for dealing with missing values or patients who withdraw prior to completing the study.

Objective tumor response rates will be calculated with a 2-sided 95% confidence interval (CI). Exploratory analysis with Chi-square tests to examine the relationship between clinical responses and treatment will be performed.

8.2.6 *Sample size calculation and Interim Analysis.*

From historical data(Edward B Garon, 2014) (Socinski, Checkmate 026, EMSO 2016; Hellman et al, Keynote 001, WCLC, 2015;), we will consider 25% response rate as not warranting further study. We will use 45% response rate as a promising result to pursue further study. In other words, we are interested in at least 20% (45% vs. 25%) improvement in treatment efficacy for arms B versus A. For each arm, using a Simon Mini-Max two-stage design with 10% type I error rate and 10% type II error rate, 23 patients will be enrolled in the first stage of the trial. If 5 or fewer patients respond, the treatment will be stopped. If 6 or more patients show a response, 16 additional patients (a total of 39 patients per group) will be enrolled. If the total number responding is 13 or less, we will conclude that the treatment is not effective. A total sample size will be 78 patinets if both arms finish the 2nd stage. If both arms fail at the first or second stage, the trial will stop. No winner will be claimed. The sample size will be 46 if both arms fail at the first stage and 62 if only one arm fails at the first stage. If only one arm pass the second stage, the arm will be the winner. If both arms pass the second stage, we will use the posterior probability, $Pr(B > A)$, (probability of the response rate in arm B higher than in arm A) to select the winner. A non-informative prior of beta distribution, beta(1,1) in both arms will be used to calculate the posterior probability. Arm B will be claimed as the winner if $Pr(B > A) > \delta = 0.8$.

8.3 Operating Characteristics

The operating characteristics of the design is evaluated by simulation (10000 times) using R software (www.r-project.org) with "clinfun" package. In particular, we are interested in the probability of (correctly) selecting an arm as superior to the other arm if it is truly superior, and conversely, the probability of (incorrectly) selecting an arm that is no better than the other arm.

8.4 Power Analysis

Power: Assuming that the true probabilities of response in arms B and A are 45% and 25%, respectively (scenario 1: 20% difference of response rate), the overall probability (power) of correctly choosing arm B as superior is 87% on the basis of superiority shown at the end of the trial. The probability of stopping arm A early and declaring arm B superior at the end of the trial is 83%. There are 7% of both arms passing the second stage with 3% claiming arm B as the winner by the Bayesian posterior probability. In a 15% difference of response rate, the overall power is 69% and 77% for the comparison of arms B and A with 40% versus 25% (scenario 2) and 45% versus 30% (scenario 3), respectively. Proportion of both arms passing the 2nd stage is 6% in scenario 2 (scenario 3: 22%), with 2% (scenario 3: 9%) claiming arm B as the winner by the Bayesian posterior probability.

8.5 Type I error

Type I error: In the null hypothesis of a 25% response rate in both arms, there are 8% misclassifying arm B as winner (i.e., 8% type I error). Among them, only 1% has both arms passing the 2nd stage, and less than 0.01% misclassify arm B as winner.

8.6 Summary

Summary: With δ=0.8, the design has a 87% power to detect a 20% difference of response rate. The power decreases to a range of 69-77% to differentiate a 15% difference of response rate. The type I error is controlled at 8% when both arms have a 25% response rate.

8.7 Table of Power Analysis

Scenario 1: Arm B=0.45 versus Arm A=0.25 (Overall power of Arm B= 87%)

	B.fail.stage1	B.fail.stage2	B.pass
A.fail.stage1	0.01	0.04	0.43
A.fail.stage2	0.01	0.03	0.41
A.pass	0	0.01	0.07

Both arms passing the 2nd stage: 7%. Among them, Arm B claims 3.05% as winner

Overall power of Arm B= 87%

Scenario 2: Arm B=0.4 versus Arm A=0.25 (Overall power of Arm B= 69%)

	B.fail.stage1	B.fail.stage2	B.pass
A.fail.stage1	0.03	0.09	0.35
A.fail.stage2	0.03	0.09	0.33
A.pass	0	0.02	0.06

Both arms passing the 2nd stage: 6%. Among them, Arm B claims 1.62% as winner

Overall power of Arm B= 69%

Scenario 3: Arm B=0.45 versus Arm A=0.3 (Overall power of Arm B= 77%)

	B.fail.stage1	B.fail.stage2	B.pass
A.fail.stage1	0	0.02	0.24
A.fail.stage2	0.01	0.04	0.43
A.pass	0	0.02	0.22

Both arms passing the 2nd stage: 22%. Among them, Arm B claims 9.14% as winner

Overall power of Arm B= 77%

Scenario 4: Arm B=0.25 versus Arm A=0.25 (Type I error= 8.06%)

	B.fail.stage1	B.fail.stage2	B.pass
A.fail.stage1	0.22	0.21	0.04
A.fail.stage2	0.22	0.19	0.04
A.pass	0.04	0.04	0.01

Both arms passing the 2nd stage: 1%. Among them, Arm B claims 0.01% as winner

Type I error= 8.06%

8.7.1 *Statistical plan for immunogenicity profiles in phase Ib and phase II:*

Phase Ib expansion cohort (PD-1 pretreated: N=18).

Two gene signatures (NF-kB, 12-chemokine genes) will be evaluated to test if they can predict the response to PD-1 blockade + HDACi treatment using the pre-treatment biopsy. For each gene signature, PCA will be used to calculate an index score based on the first principal component. The derived gene signature score will be then used to test if the response group has a higher score than the non-response group using the two-sample t test. A sample size of 18 patients will give an 80% power to detect an effect size of 1.6 with a two-sided 5% type error if the response rate is 30% (i.e., 5 responders and 13 non-

responders) by the two-sample t test. If the response rate is 40% (i.e., 7 responders and 11 non-responders), the power will increase to 87%. We will also test the difference of the score from pre to post-treatment between the responders and non-responders using two-sample t-test. With this sample size (n=18) and 80% power, it will be able to detect an effect size of 1.57 and 1.45 for a response rate of 30% and 40%, respectively with a two-sided 5% type error by the two-sample t-test. In addition, we will also determine association of individual genes with response or resistance, including T cell co-stimulatory and inhibitory genes.

Phase II cohort (PD-1 naïve).

We would like to know if these gene signatures in pre-treatment biopsies could predict a differential treatment effect. That is, could patients with high gene signature score result in a higher response rate to anti-PD-1 but patients with either low or high respond to anti-PD-1+HDACi? A logistic regression model will be used to evaluate this hypothesis by testing an interaction effect model, which includes two main effects, gene signature score and treatment status, and their interaction term. We will also test the difference of the score from pre to post-treatment between the two treatment groups using two-sample t-test.

9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

9.1 Investigational Product

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

Clinical Supplies will be provided by Merck as summarized in Table 16.

Table 16. Product Descriptions

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

9.2 Packaging and Labeling Information

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

9.3 Clinical Supplies Disclosure

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

9.4 Storage and Handling Requirements

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label.

Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site.

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

9.5 Returns and Reconciliation

The investigator is responsible for keeping accurate records of the clinical supplies received from Merck or designee, the amount dispensed to and returned by the subjects and the amount remaining at the conclusion of the trial.

Upon completion or termination of the study, all unused and/or partially used investigational product will be destroyed at the site per institutional policy. It is the Investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

10.0 DATA SAFETY MONITORING PLAN

10.1 Risk to Subjects

10.1.1 *Human subject involvement and characteristics*

Human subjects who have the diagnosis of advanced NSCLC are eligible to participate in the clinical trial described in this proposal. The risk to subjects will be outlined clearly and in detail in the informed consent. Women who are pregnant are not eligible.

10.2 Recruitment and Informed Consent

Patients who present to the Thoracic Oncology Program at the Moffitt Cancer Center or the OSU Thoracic Clinics who have advanced NSCLC are offered participation in the clinical trial described in this proposal. The trial is explained in detail to the patients by one of the investigators on the trial. The patients are given the opportunity to read the informed consent document and are given a chance to ask questions. If they wish to participate the patient will then sign the informed consent document in the presence of a witness. The

study team member who participates in the informed consent process also documents, in a clinic note, the nature of the consent process that occurred.

10.3 Protection Against Risk

To protect participants from excess risk, the above-mentioned study procedures and dose-escalation scheme were instituted. Additional protection is provided through the data safety and monitoring plan described below. The complete care of each patient, including the clinical management of all toxicities, is provided to the patient by physicians at the Moffitt Cancer Center. The clinical data are kept in the patient's individual electronic hospital record. Research study documentation charts are kept in a locked secure room with limited access and through Oncore (a Web-based, password-protected database), with privacy protected to the full extent of the law. Authorized research investigators, the Department of Health and Human Services, and the Institutional Review Board may inspect the records. Final protocol and ICF approvals will be obtained from the IRB.

Additional protection is provided through the data safety and monitoring plan described below.

10.4 Importance of the Knowledge to be Gained

The development of a well-tolerated and effective regimen in a disease could potentially at worst add to the armamentarium of available regimens and at best change standard of care. Specific strategies to improve the care of patients relapsing following chemotherapy for lung cancer are direly needed.

10.5 Data Safety and Monitoring Plan

The Data Safety & Monitoring Plan (DSMP) will ensure that this trial is well designed, responsibly managed, appropriately reported, and that it protects the rights and welfare of patients. The following internal and external review and monitoring processes provide oversight and active monitoring of this trial:

- The Principal Investigators (PI)
- The Clinical Trials Office (CTO)
- The Scientific Review Committee (SRC)
- The Protocol Monitoring Committee (PMC);
- Institutional Review Board (IRB).

The protocol includes a section that specifies the following with respect to Adverse Event reporting: what constitutes an adverse event (versus what is a serious adverse event), the entities to which adverse events should be reported, the timing of this reporting, and the person or persons responsible for reporting. This includes prompt (within one day of

knowledge of the event) reporting to the IRB for unanticipated risks to subjects and reporting in writing within five working days to the IRB and sponsor.

10.6 Scientific Review Committee (SRC)

The two Therapeutic boards of the SRC meet every other week one on the first Wednesday and the second one meets on the third Thursday of every month.

Each SRC conducts a formal internal peer review of all clinical protocols and general scientific oversight of interventional clinical research. Protocols are reviewed for scientific merit, adequate study design, safety, availability of targeted study population, and feasibility of timely completion of all proposed research projects to be conducted by its assigned programs at each Cancer Center. The SRC is responsible for evaluating the risk/benefit assessment and corresponding data and safety monitoring plan as part of the scientific review and approval process.

10.7 PI Responsibility

The PI of each study is ultimately responsible for every aspect of the design, conduct and actions of all members of the research team. This includes the final analysis of the protocol.

All protocols include a DSMP and procedures for its implementation commensurate with the risk and complexity of the study. The DSMP must include a structured adverse event determination, monitoring and reporting system, including standardized forms and procedures for referring and/or treating subjects experiencing adverse events. The plan must include data and safety-monitoring procedures for subjects enrolled who may be receiving a part of their protocol-required treatment at community sites.

In all cases, the PI of the study will have primary responsibility for ensuring that the protocol is conducted as approved by the SRC and IRB. The PI will ensure that the monitoring plan is followed, that all data required for oversight of monitoring are accurately reported to a DSMB and/or to the PMC and IRB as required, that all adverse events are reported according to protocol guidelines, and that any adverse actions reflecting patient safety concerns are appropriately reported.

10.8 The Protocol Monitoring Committee (PMC)

The PMC meets once a month. The PMC reviews and evaluates safety and/or efficacy data for all physician authored clinical intervention trials. The PMC ensures the safety of patients and the validity and integrity of data. PMC reviews SAEs, deviations, Interim analysis, interim and final reports from the external Data Monitoring Committee (DMC) as well as audits both internally and externally. The PMC can make the following determinations, Accepted, Acceptable with Corrective Action and Tabled.

Investigators of studies, which are designated to be reviewed by the PMC for data and safety monitoring, shall provide an interim analysis report of the study's progress and summary of adverse events and deviations based on the phase of the study and the associated risk of the study or more often if applicable. The external DSMB (if applicable) shall forward its report for high-risk studies designated for external review at least annually or more often if applicable.

10.9 Suspension/Termination

The PMC and/or the IRB may vote to suspend or terminate approval of a research study not being conducted in accordance with the IRB, the Cancer Center and/or regulatory requirements or that has been associated with unexpected problems or serious harm to subjects. The PMC/IRB will notify the PI in writing of such suspension or terminations. It is the responsibility of the PMC/IRB Chairperson to ensure prompt written notification of any suspensions or terminations of PMC/IRB approval to the relevant Federal Agencies, including OHRP, FDA, the study sponsor/funding source and if applicable, the Affiliate Program.

10.10 Trial Discontinuation

For reasonable cause the Investigator and/or sponsor may terminate this study prematurely. Conditions that may warrant termination include, but are not limited to: the discovery of an unexpected, significant, or unacceptable risk to the patients enrolled in the study or if the accrual goals are met. A written notification of termination will be issued.

10.11 Monitoring of the Study and Regulatory Compliance

The Principal Investigator and the Clinical Research Coordinator assigned to the case will be primarily responsible for maintaining all study related documents including the clinical research forms. Oncore is the database of record for all CRF entries and will be verified with source documentation. The review of medical records within PowerChart will be done in a manner to assure that patient confidentiality is maintained.

10.12 Internal Monitoring Plan

Data will be captured in Oncore, Moffitt's Clinical Trials Database.

Regulatory documents and case report forms will be reviewed routinely by the MCC Clinical Research Monitoring Core for accuracy, completeness and source verification of data entry, validation of appropriate informed consent process, adherence to study procedures, and reporting of SAEs and protocol deviations according to MCC Monitoring Policies.

10.13 Protocol Modifications

No modifications will be made to the protocol without the agreement of the investigators. Changes that significantly affect the safety of the patients, the scope of the investigation, or the scientific quality of the study will require Scientific Review Committee and Institutional Review Board approval prior to implementation, except where the modification is necessary to eliminate apparent immediate hazard to human subjects. Any departures from the protocol must be fully documented in the case report form and the source documentation.

10.14 The Institutional Review Board (IRB)

The trial will not be initiated without approval of the appropriate Institutional Review Board (IRB). All administrative requirements of the governing body of the institution will be fully complied with. This protocol, consent procedures, and any amendments must be approved by the IRB in compliance with current regulations of the Food and Drug Administration. A letter of approval will be sent to the institution(s) funding the study prior to initiation of the study and when any subsequent modifications are made. The IRB will be kept informed by the investigator as to the progress of the study as well as to any serious or unusual adverse events.

10.15 Patient Privacy

In order to maintain patient confidentiality, all case report forms, study reports and communications relating to the study will identify patients by initials and assigned patient numbers. The US Food and Drug Administration (FDA) may also request access to all study records, including source documentation for inspection.

10.16 Records Retention

U.S. FDA regulations (21 CFR §312.62[c]) require that records and documents pertaining to the conduct of this study and the distribution of investigational drug, including CRFs, consent forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for 2 years after marketing application approval. If no application is filed, these records must be kept 2 years after the study is discontinued and the U.S. FDA and the applicable national and local health authorities are notified.

10.17 Compliance with Trial Registration and Results Posting Requirements

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

11.0 APPENDICES

11.1 ECOG Performance Status

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

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

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

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

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

* As published in the European Journal of Cancer:

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

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

11.4 See Events of Clinical Interest Guidance Document

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