CITY OF HOPE
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DEPARTMENT OF HEMATOLOGY AND HEMATOPOIETIC CELL TRANSPLANTATION

TITLE: A Phase 1 Study of Pembrolizumab Plus Vorinostat for Relapsed or Refractory Diffuse Large B-cell Lymphoma, Follicular Lymphoma, and Hodgkin Lymphoma

CITY OF HOPE PROTOCOL NUMBER/VERSION: IRB # 17080 Protocol Date 10/16/20

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COH Amendment 04	(Protocol v03 dated 11/22/2017)	Version: 04
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COH Amendment 14	(Protocol v10 dated 10/16/20)	Packet: 14

DISEASE SITE: Diffuse Large B-cell Lymphoma, Follicular Lymphoma, and Hodgkin Lymphoma

STAGE: Relapsed/Refractory

MODALITY(IES):

TYPE: Phase 1

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Clinical Trial Protocol

A Phase 1 Study of Pembrolizumab Plus Vorinostat for Relapsed or Refractory Diffuse Large B-cell Lymphoma, Follicular Lymphoma, and Hodgkin Lymphoma

Version Date:	10/16/20
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1.0 TRIAL SUMMARY

Protocol Title:
A Phase I Study of Pembrolizumab Plus Vorinostat for Relapsed or Refractory Diffuse Large B-cell Lymphoma, Follicular Lymphoma, and Hodgkin Lymphoma
Brief Protocol Title for the Lay Public (if applicable):
Pembrolizumab Plus Vorinostat for Treatment of Relapsed or Refractory Lymphomas
Study Phase:
I, with an expansion cohort
Participating Sites:
- City of Hope
Rationale for this Study:
Diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma (FL) are the most common B-cell non-Hodgkin lymphomas (NHL), which together comprise the majority of NHLs.[1] Classical Hodgkin lymphoma (HL) is also a lymphoma of B-cell origin that accounts for about 10% of all lymphomas.[1] While upfront therapy for DLBCL and HL cures the majority of patients, about 20-40% of patients will have relapsed or refractory (rel/ref) disease.[2] Standard of care treatment for rel/ref DLBCL and HL is salvage chemotherapy followed by autologous stem cell transplantation (ASCT). However, this approach only cures about a third to half of eligible patients.[3] DLBCL and HL patients who are refractory to second-line therapy or relapse after ASCT have dismal outcomes.[4] Unlike DLBCL and HL, the great majority of FL patients are incurable with standard therapy. Agents used to treat FL in the second-line and beyond typically lead to shorter remissions.[5] Improved therapies for patients with rel/ref HL, DLBCL, and FL are urgently needed. The programmed death receptor-1 (PD-1) pathway is an immune checkpoint that normally serves to dampen immune responses in tissues. PD-1 is expressed on activated T-cells and binds its ligands, PD-L1 and PD-L2, on tissue cells or antigen presenting cells to decrease T-cell activation, proliferation, and survival.[6] Tumor cells can co-opt this pathway to evade attack by the host immune system.[6] A wide range of hematologic malignancies express PD-1 or PD-L1, including HL,[7] DLBCL,[8] and FL.[9] In addition, molecular analyses have demonstrated that genetic alterations involving PD-L1 and PD-L2 are critical in the pathogenesis of HL and subtypes of DLBCL.[7, 10] Monoclonal antibody inhibitors of PD-1 have produced clinical responses in early-phase studies in patients with a range of lymphomas, including HL, DLBCL, and FL. A PD-1 inhibitor, pidilizumab, produced responses as a single-agent in patients with rel/ref FL and HL,[11] and yielded a 66% overall response rate (ORR) when used in combination with rituximab in patients with rel/ref FL.[12] In a phase Ib study of another PD-1 inhibitor, pembrolizumab, in hematologic malignancies, a 66% ORR was observed in patients with

HL who had failed prior brentuximab vedotin.[13] Similarly, in a phase I study of the PD-1 inhibitor, nivolumab, an 87% ORR and 100% clinical benefit rate was observed in patients with relapsed or refractory HL,[14] along with a 36% ORR in relapsed or refractory DLBCL, and a 40% ORR in relapsed or refractory FL.[15]

Although responses to PD-1 inhibitors have been observed in patients with HL, DLBCL, and FL, there is room for improvement. Despite the high response rate observed to single-agent PD-1 inhibition, the complete response (CR) rate in patients with HL appears to be only 10-20%[14] and is only 5-10% in patients with DLBCL or FL.[15] The addition of a synergistic agent with PD-1 inhibition may enhance anti-tumor activity and result in deeper and more durable responses. An attractive combination partner is vorinostat, a histone deacetylase inhibitor (HDACi), which has demonstrated activity in a range of lymphomas, including HL, DLBCL, and FL.[16, 17 18-21]

HDACi therapy has many immunologic effects on tumor cells and immune effector cells that may enhance the effect of PD-1 blockade when given in combination. HDACis immunomodulate tumor cells, by increasing expression of tumor-associated antigens, upregulating genes that control antigen presentation machinery, and promoting release of mediators of immunogenic cell death.[22] HDACis also have important effects on immune cells, including enhancing CD8+ cytotoxic T-lymphocyte (CTL) function, decreasing regulatory T-cell numbers and function, and modulating myeloid-derived suppressor cell (MDSC) differentiation.[22] Most notably, **there is evidence that HDAC inhibition combined with PD-1/PD-L1 pathway blockade results in enhanced anti-tumor activity in preclinical models.** HDACis directly upregulate PD-L1 expression in melanoma cell lines, murine models, and patient tumor samples.[23] Indeed, combined HDAC and PD-1 inhibition results in synergistic killing of tumor cells and HDACis reverse tumor resistance to checkpoint blockade in pre-clinical murine breast and colorectal cancer models.[24] Zheng et al. found that HDAC inhibition with romidepsin increases *in vitro* PD-L1 expression in lung cancer cell lines, promotes T-cell infiltration into lung cancers, and enhances function of recruited T-cells in a mouse model. In mice inoculated with lung cancer tumor cells, combined romidepsin and anti-PD-1 therapy significantly reduced tumor growth compared to HDAC or PD-1 inhibition alone.[25] The authors chose to study romidepsin based on a screen of drugs that could induce T-cell chemokine expression, but the authors also demonstrated in the study that vorinostat had similar effects. In a separate study using a murine model of lung cancer, vorinostat increased CD8+ T-cell infiltration into tumors.[26] In light of the observation that non-responders to anti-PD-1 therapy have a deficiency of tumor infiltrating T-cells in pre-treatment tumor biopsies,[27] the ability of vorinostat and HDACis to increase T-cell recruitment into tumors and to induce PD-L1 expression on tumor cells, as well as the ability of HDACis to synergize with anti-PD-1 therapy suggests that vorinostat may be an ideal agent to combine with a PD-1 inhibitor to increase the frequency and depth of responses in lymphoma patients. We will conduct a phase I study with an expansion cohort to evaluate the safety and obtain a preliminary estimate of the efficacy of combining pembrolizumab with vorinostat for the treatment of rel/ref HL, DLBCL, and FL.

Objectives:

Primary Objectives:

In adults with relapsed or refractory DLBCL, FL, or HL:

- To assess the safety and tolerability of vorinostat plus pembrolizumab therapy by evaluation of toxicities including: type, frequency, severity, attribution, time course and duration.

- To determine the maximum tolerated dose (MTD) and the recommended phase II dose (RP2D) of vorinostat when given in combination with pembrolizumab.

Secondary Objectives:

- To obtain preliminary estimates of the anti-tumor activity of pembrolizumab plus vorinostat therapy by assessing the overall response rate (ORR), complete response (CR) rate, duration of response (DOR), overall survival (OS) and progression-free survival (PFS).

Exploratory Objectives:

- To evaluate responses according to the Lymphoma Response to Immunomodulatory therapy Criteria (LYRIC).[28]

- To explore genomic biomarkers of response and resistance to pembrolizumab plus vorinostat therapy in patients with DLBCL, FL, or HL.

- To explore immunologic biomarkers of response and resistance to pembrolizumab plus vorinostat therapy in patients with DLBCL, FL, or HL.

- To explore the value of circulating DNA (ctDNA) as a biomarker of response to pembrolizumab plus vorinostat therapy.

- To explore the association between baseline total metabolic tumor volume, complete response, and PFS after pembrolizumab plus vorinostat therapy in patients with HL or DLBCL.

- To explore the association between change in total metabolic tumor volume between baseline and 12 weeks, complete response, and PFS after pembrolizumab plus vorinostat therapy in patients with HL or DLBCL.

- To explore the association between outcomes (overall response, complete response, PFS) and other baseline quantitative PET (qPET) parameters including total lesion glycolysis and SUVmax in patients with HL or DLBCL.

Study Design:

This is a prospective, single-arm, open-label phase I study of pembrolizumab (MK-3475) plus vorinostat in subjects with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), or classical Hodgkin lymphoma (HL) that have failed at least one prior line of therapy. Eligible subjects must have: 1. Recurrence of disease after a documented complete response (CR); 2. Progression of disease after a partial response (PR) to the prior regimen; 3. Partial response, stable disease (SD) or progressive disease (PD) with evidence of measurable residual disease at the completion of the prior treatment regimen.

This phase I trial will implement a modified rolling six dose escalation design, a more conservative version of the rolling six design of Skolnik, et al. for enrollment with dose escalation, de-escalation, or expansion of a cohort on the basis of the occurrence of dose limiting toxicities (DLTs).[29] An estimated 52 subjects will be enrolled on this study to evaluate the safety and tolerability of combined pembrolizumab and vorinostat therapy. The study will consist of a dose-escalation portion and an expansion cohort of 40 patients to obtain additional safety data regarding the study combination. In the dose-escalation portion of the study, vorinostat will be dosed according to the assigned dose level. In the expansion cohort, subjects will receive vorinostat at the RP2D. In both the dose-escalation and expansion cohort portions of the study, subjects will receive pembrolizumab 200mg intravenously every 3 weeks. Cycle length will be 21 days. Study treatment will continue for a maximum of 24 months, or until progressive disease (PD), unacceptable toxicity, withdrawal of consent, pregnancy of the subject, non-compliance, or administrative reasons. Subjects will have disease re-assessment after every 4 cycles. Subjects who achieve documented CR with study therapy may consider study treatment discontinuation after receiving 2 additional cycles of study therapy beyond documentation of CR and at least 24 weeks total of therapy.

At the end of treatment, each subject will be followed for 30 days for adverse event monitoring (90 days for severe adverse events and events of clinical interest). Subjects who discontinue treatment for reasons other than disease progression will have post-treatment follow-up for disease status until disease progression, initiation of a new anti-cancer therapy, withdrawal of consent, or becoming lost to follow-up.

The primary objective of the trial is to evaluate the safety and tolerability of combined pembrolizumab and vorinostat therapy in subjects with relapsed or refractory DLBCL, FL, or HL. The dose escalation portion of the study will evaluate the safety and tolerability of the study regimen, establish the maximum tolerated dose (MTD), and determine the recommended Phase II dose (RP2D). Through the expansion cohort, we will obtain additional safety information, including information about any delayed toxicities, and we will obtain a preliminary estimate of the efficacy of the combination in subjects with relapsed or refractory DLBCL, FL, or HL, as assessed by the overall response rate (ORR). The complete response (CR) rate, duration of response (DOR), overall survival (OS) and progression-free survival (PFS) will also be studied. Response assessments will be

performed by investigators using the 2014 Lugano Classification and as a secondary endpoint we will evaluate the responses according to the LYRIC criteria. Immunologic and genomic biomarkers of response and resistance to study therapy will be explored.

Endpoints:

- Primary Endpoint: Toxicity

- Secondary Endpoints: Overall response rate (ORR), complete response (CR) rate, time to response (TTR), duration of response (DOR), overall survival (OS) and progression free survival (PFS).

Sample Size/Number of Trial Subjects:

Expected sample size will be 52 evaluable patients (12 in the dose-escalation portion of the study, and 40 in the expansion cohort). The minimum sample size is 6 evaluable patients. Considering replacement of inevaluable patients, the maximum study accrual is set at 60 patients.

Estimated Duration of the Study

Estimated Enrollment Period: 48 months

Estimated Duration of Trial: 72 months

Duration of Participation: Subjects will participate in the trial from the time the subject signs informed consent through the final protocol-specified study activity. Following the screening phase (28 days or less), eligible subjects will be enrolled and will receive both study agents in 21-day cycles. Study treatment will continue for a maximum of 24 months. Subjects who achieve a complete response (CR) may consider stopping study therapy early if they meet criteria for holding therapy. After the end of treatment, each subject will be followed for 30 days for adverse event monitoring (serious adverse events will be collected for 90 days after the end of treatment). Subjects who discontinue for reasons other than disease progression will have post-treatment follow-up for disease status until disease progression, initiating a non-study new anti-cancer therapy, withdrawing consent, or becoming lost to follow-up.

Summary of Subject Eligibility Criteria:

<u>Inclusion Criteria</u>:

Eligible patients must:

- Have a histologically confirmed diagnosis of follicular lymphoma, diffuse large B-cell lymphoma, or classical Hodgkin lymphoma according to the WHO classification, with hematopathology review at the participating institution.
    - FL: grade 1, 2, 3A, or 3B are eligible.
    - DLBCL: subtypes of DLBCL including transformed indolent lymphomas (TIL), primary mediastinal large B-cell lymphoma

(PMBCL), and aggressive B-cell lymphoma unclassified (BCL-U) are eligible.

- HL: all classical HL subtypes are eligible except for nodular lymphocyte predominant Hodgkin lymphoma, which is excluded.

NOTE: Per Amendment (Protocol V9 dated 06-04-20), this study will only enroll HL patients who have had prior exposure to PD-1/PD-L1 immunotherapy. FL, DLBCL, and HL patients without prior exposure to PD-1/PD-L1 immunotherapy are no longer eligible.

- Patients with HL or DLBCL must refuse or not be candidates for curative autologous stem cell transplantation.
- Have relapsed or refractory disease after at least 1 prior regimen, including:
  - Recurrence of disease after a documented complete response (CR).
  - Progression of disease after a partial response (PR) to the prior regimen.
  - Partial response (PR), stable disease (SD) or progressive disease (PD) at the completion of the prior treatment regimen. If a patient has PR to prior regimen without PD, there must be biopsy-proven residual disease that is measurable.

NOTE: Per Amendment (Protocol V10 dated 10-16-20), this study will only enroll HL patients who are *refractory* to PD-1/PD-L1 immunotherapy.
Refractory to PD-1/PD-L1 immunotherapy is defined as patients who had prior exposure to PD-1/PD-L1 immunotherapy and either - achieved a best response of SD or PD or - achieved a best response of CR/PR but developed PD while on active PD-1/PD-L1 treatment.

1. Documented informed consent of the participant or legally authorized representative.
2. Be ≥ 18 years of age on day of signing informed consent.
3. Have measurable disease by CT or PET scan, with one or more sites of disease ≥ 1.5cm in longest dimension.
4. Be willing to provide tissue from a fresh core or excisional biopsy of a tumor lesion prior to starting study therapy or from archival tissue of a biopsy that was performed after the most recent systemic therapy.
5. Have a performance status of 0 or 1 on the ECOG Performance Scale.

6. Demonstrate adequate organ function as defined in Table 1, all screening labs should be performed within 14 days of treatment initiation.

7. 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.

Exclusion Criteria:

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

1. Is currently participating and receiving study therapy or has participated in a study of an investigational agent and received study therapy or used an investigational device within 3 weeks of the first dose of treatment.
2. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment.
3. Has received prior allogeneic hematopoietic stem cell transplant within the past 5 years, requires immunosuppression, or has evidence of active graft-versus-host-disease.
4. Has received prior autologous hematopoietic stem cell transplant within the last 60 days.
5. Has a known history of active TB infection (Bacillus Tuberculosis).
6. Hypersensitivity to pembrolizumab or any of its excipients.
7. Has had a prior anti-cancer monoclonal antibody (mAb) within 3 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 3 weeks earlier. If a patient has progressive or stable disease to prior regimen, rituximab is allowed up to 2 weeks prior to the initiation of study therapy.
8. Has had prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to a previously administered agent.
    - Note: Subjects with ≤ Grade 2 neuropathy are an exception to this criterion and may qualify for the study.
    - Note: If subject received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.
9. Has taken valproic acid, or another histone deacetylase inhibitor, within 2 weeks prior to study Day 1.

10. 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.
11. Has known active central nervous system (CNS) involvement by lymphoma, including parenchymal and/or lymphomatous meningitis. Subjects with prior CNS involvement by lymphoma must have a baseline MRI and lumbar puncture at screening that demonstrate no active lymphoma in the CNS.
12. Has active autoimmune disease that has required systemic treatment in the past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (eg., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment. Hemolytic anemia associated with the lymphoma does not exclude a patient from the study.
13. Has a history of (non-infectious) pneumonitis that required steroids or current pneumonitis.
14. Has an active infection requiring systemic therapy.
15. Has a mean QT interval corrected for heart rate (QTc) ≥ 470 ms calculated from 3 electrocardiograms (ECGs) using Fridericia formula.
16. Is unable to swallow capsules, has a partial or small bowel obstruction, or has a gastrointestinal condition resulting in a malabsorptive syndrome (e.g. small bowel resection with malabsorption).
17. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.
18. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.
19. 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.
20. Has a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).
21. Has known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected).
22. Has received a live vaccine within 30 days of planned start of study therapy.

Investigational Product Dosage and Administration:

Pembrolizumab 200mg IV Q3weeks.

Vorinostat 100mg capsules PO according to dose level.

Clinical Observations and Tests to be Performed:

- Full medical history and demographics
- Complete physical exam

- ECOG Performance Status
- Vital signs, weight and height, and oxygen saturation
- 12-lead ECG
- Buccal swab
- Bone marrow aspirate and biopsy (not for all patients: specific requirements are provided in study calendar and footnote j).
- Tumor biopsy
- Review of prior and concomitant medications
- PET-CT or IV contrast-enhanced CT scan of neck, chest, abdomen, pelvis of diagnostic quality (and/or MRI for lesions not well-visualized by CT). Clinical laboratory tests for:
    - Hematology
    - Serum chemistry
    - Thyroid function panel
    - Coagulation (PT, PTT, INR)
    - Serum or urine pregnancy test (for women of childbearing potential who have not been free from menses for > 1 year)
    - Urinalysis

Refer to the Study Flow Chart (section 8.1) for a detailed schedule of these activities.

Statistical Considerations:

This is a phase I study, including dose-escalation and expansion portions of the study. The dose-escalation will have 2 dose levels and 2 possible de-escalation dose levels, for a total of 4 possible dose levels. Patients will be treated according to dose level assignment. In the expansion portion of the study, subjects will receive therapy at the RP2D.

The dose-escalation portion of the trial will employ a modified Rolling 6 design, a more conservative version of the Rolling 6 design of Skolnik, et al [29]. In this design, at most, 3 patients will be under observation for DLT on the current test dose level at any time. Patients who are not evaluable for DLT will be replaced. Once each patient is evaluable for toxicity and passes without a DLT, an additional patient *may* be accrued on that dose level -up to 6 patients. Once 3 patients are evaluable with no patient at that dose level experiencing a DLT, the dose can be escalated, or up to 3 additional patients may be treated at the current dose level. Although this design does not require that 6 patients be treated, no more than 6 evaluable patients will be accrued to any dose level during the dose finding portion of this study. If at any time, the dose level has 1 documented DLT with fewer than 6 evaluable patients, accrual will continue until 6 patients are evaluable. Escalation will terminate as soon as two or more patients experience any DLT attributable to the study treatment, at a given dose level. MTD will be declared at the highest dose level at which 6

patients have been treated and at most 1/6 patients experiences DLT. If more than 1/6 patients experiences DLT, then the next lower dose will be expanded. There will be no intrapatient dose escalation.

Patient demographic and baseline characteristics, including age, gender, medical history, and prior therapy, will be summarized using descriptive statistics. For continuous variables, descriptive statistics (number [n], mean, standard deviation, standard error, median (range)) will be provided. For categorical variables, patient counts and percentages will be provided.

Observed toxicities will be summarized by type (organ affected or laboratory determination such as absolute neutrophil count), severity (by NCI CTCAE v4.03 and nadir or maximum values for lab measures), date of onset, duration, reversibility, and attribution. Tables will be constructed to summarize the observed incidence by severity and type of toxicity.

ORR will be calculated as the proportion of evaluable patients that have confirmed CR or PR, as defined according to the 2014 Lugano Classification, exact 95% confidence intervals will be calculated for these estimates. CR rate will be similarly estimated. Response rates will also be evaluated based on number and type of prior therapy(ies). Duration and time to response (DOR and TTR), as well as overall survival (OS) and progression-free survival (PFS) will be estimated using the product-limit method of Kaplan and Meier.

Because of the unique immune-related adverse events (IrAEs) observed with checkpoint inhibitors, we will monitor for "unacceptable toxicity" with this new combination of drugs (defined in Section 10.2). The expected rate of "unacceptable toxicity" should not be ≥33%. The early stopping rule for unacceptable toxicity will be assessed after enrollment of 12 patients (total, across cohorts) treated at the RP2D and will be assessed once the 12th patient has completed at least 4 cycles of therapy. If >3 "unacceptable toxicity" events occur in the first 12 patients (≥33%) treated (across disease subtypes) at RP2D, or at a rate ≥33% thereafter at the quarterly review, accrual will be halted and a full review of these events will be performed by the City of Hope Data Safety Monitoring Committee (DSMC). Patient accrual will not resume until approved by the DSMC to do so. These rules are in addition to the quarterly review of all toxicities submitted to the City of Hope Data Safety Monitoring Committee (DSMC). Patients with ongoing toxicity will be followed until resolution or stability.

Sponsor/Licensee:
Investigator-initiated trial at City of Hope Supported by Merck, Inc.
Case Report Forms
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2.0 TRIAL DESIGN

2.1 Trial Design

This is a prospective, single-arm, open-label phase I study of pembrolizumab (MK-3475) plus vorinostat in subjects with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), or classical Hodgkin lymphoma (HL) that have failed at least one prior line of therapy. Eligible subjects must have: 1. Recurrence of disease after a documented complete response (CR); 2. Progression of disease after a partial response (PR) to the prior regimen; 3. Partial response, stable disease (SD) or progressive disease (PD) with evidence of measurable residual disease at the completion of the prior treatment regimen. If a patient has PR to prior regimen without PD, there must be biopsy-proven residual disease that is measurable.

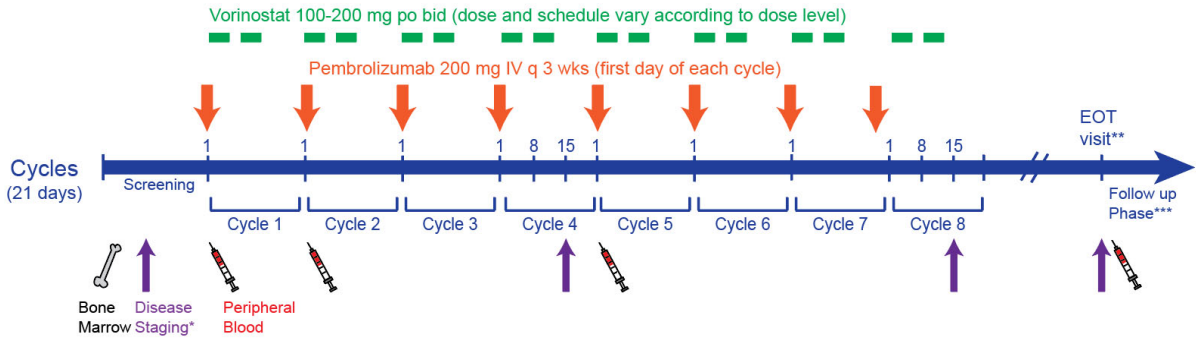
An estimated 52 subjects will be enrolled on this study to evaluate the safety and tolerability of combined pembrolizumab and vorinostat therapy. The study will consist of a dose-escalation portion and an expansion cohort of 40 patients to obtain additional safety data regarding the study combination. In the dose-escalation portion of the study, vorinostat will be dosed according to the assigned dose level. In the expansion cohort, subjects will receive vorinostat at the recommended Phase II dose (RP2D). In both the dose-escalation and expansion cohort portions of the study, subjects will receive pembrolizumab 200mg intravenously every 3 weeks. Cycle length will be 21 days. Study treatment will continue for a maximum of 24 months, or until progressive disease (PD), unacceptable toxicity, withdrawal of consent, pregnancy of the subject, non-compliance, or administrative reasons. Subjects will have disease re-assessment after every 4 cycles. Subjects who achieve documented CR with study therapy may consider study treatment discontinuation after receiving 2 additional cycles of study therapy beyond documentation of CR and at least 24 weeks total of therapy.

At the end of treatment, each subject will be followed for 30 days for adverse event monitoring (90 days for severe adverse events and events of clinical interest). Subjects who discontinue treatment for reasons other than disease progression will have post-treatment follow-up for disease status until disease progression, initiation of a new anti-cancer therapy, withdrawal of consent, or becoming lost to follow-up.

The primary objective of the trial is to evaluate the safety and tolerability of combined pembrolizumab and vorinostat therapy in subjects with relapsed or refractory DLBCL, FL, or HL. The dose escalation portion of the study will evaluate the safety and tolerability of the study regimen, establish the maximum tolerated dose (MTD), and determine the recommended Phase II dose (RP2D). Through the expansion cohort, we will obtain additional safety information, including information about any delayed toxicities, and we will obtain preliminary estimates of the anti-tumor activity of the combination in subjects with relapsed or refractory DLBCL, FL, or HL, as assessed by the overall response rate (ORR). The complete response (CR) rate, duration of response (DOR), overall survival (OS) and progression-free survival (PFS) will also be studied. Response assessments will be performed by investigators using the 2014 Lugano Classification. As an exploratory objective, we will also assess response

and disease progression according to the new Lymphoma Response to Immunomodulatory therapy Criteria (LYRIC) criteria (Appendix L).[28] Immunologic and genomic biomarkers of response and resistance to study therapy will be explored.

2.2 Trial Diagram



*** Disease Staging will be by either PET/CT (preferred) or CT scan, and will be performed every 4 cycles until disease progression or off study therapy (See Sections 9.2.6 and 10.1 for details). A bone marrow biopsy will be performed at screening only in FL patients and some DLBCL and HL patients according to study calendar (footnote j). Following initial screening, and unless clinically indicated, bone marrow specimens will be collected only to confirm CR, and only on patients who had bone marrow involvement at baseline.**

**** End of Treatment visit.**

***** Follow up Phase for patients who have completed treatment without disease progression will include staging every 12 weeks for the first year and every 18 weeks thereafter, until disease progression or off study.**

3.0 OBJECTIVES

In adults with relapsed or refractory DLBCL, FL, or HL:

3.1 Primary Objectives

- To assess the safety and tolerability of vorinostat plus pembrolizumab therapy by evaluation of toxicities including: type, frequency, severity, attribution, time course and duration.

- To determine the maximum tolerated dose (MTD) and the recommended phase II dose (RP2D) of vorinostat when given in combination with pembrolizumab.

3.2 Secondary Objectives

- To obtain preliminary estimates of the anti-tumor activity of pembrolizumab plus vorinostat therapy by assessing the overall response rate (ORR), complete response (CR) rate, duration of response (DOR), overall survival (OS) and progression-free survival (PFS).

3.3 Exploratory Objectives

(1) Evaluate responses and disease progression according to the Lymphoma Response to Immunomodulatory therapy Criteria (LYRIC).[28]

(2) Explore genomic biomarkers of response and resistance to pembrolizumab plus vorinostat therapy in patients with DLBCL, FL, or HL.

(3) Explore immunologic biomarkers of response and resistance to pembrolizumab plus vorinostat therapy in patients with DLBCL, FL, or HL.

(4) Explore the value of circulating DNA (ctDNA) as a biomarker of response to pembrolizumab plus vorinostat therapy.

(5) Explore the association between baseline total metabolic tumor volume, complete response, and PFS after pembrolizumab plus vorinostat therapy in patients with HL or DLBCL.

(6) Explore the association between change in total metabolic tumor volume between baseline and 12 weeks, complete response, and PFS after pembrolizumab plus vorinostat therapy in patients with HL or DLBCL.

(7) Explore the association between outcomes (overall response, complete response, PFS) and other baseline quantitative PET (qPET) parameters including total lesion glycolysis and SUVmax in patients with HL or DLBCL.

4.0 BACKGROUND & RATIONALE

4.1 Study Diseases

4.1.1 Diffuse Large B-cell Lymphoma

DLBCL is an aggressive B-cell non-Hodgkin lymphoma (NHL) and is the most common subtype of NHL in the United States. DLBCL accounts for about a quarter to one-third of cases of NHL,[1, 30] with approximately 22,000 estimated new cases and 10,000 deaths in 2013. Initial chemo-immunotherapy with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) cures about two-thirds of DLBCL patients. While the addition of rituximab to standard induction chemotherapy for DLBCL has improved cure rates after upfront treatment, it has led to inferior outcomes in the one-third of patients with relapsed or refractory (rel/ref) DLBCL.[3] Standard therapy for rel/ref DLBCL is salvage chemo-immunotherapy followed by autologous stem cell transplantation (ASCT) in chemosensitive patients. The overall response rate (ORR) after salvage chemo-immunotherapy is lower (51%) when patients have received prior rituximab, and the overall 3-year event free survival for patients with rel/ref DLBCL eligible to receive aggressive therapy (salvage chemo-immunotherapy and ASCT) who have received prior rituximab is only 21%.[3] Even among

patients who respond to salvage therapy and undergo ASCT, about half will relapse after ASCT. Outcomes in patients with DLBCL who relapse after ASCT are dismal and treatment options are limited.[4] Improved therapy for rel/ref DLBCL is urgently needed.

4.1.2 Follicular Lymphoma

Follicular lymphoma (FL) is the most common indolent non-Hodgkin lymphoma (NHL), and second most common subtype of NHL overall, accounting for approximately 20% of all NHLs.[1, 31] The median age at diagnosis in patients with FL is 60 to 65 years old. Aside from a proportion of limited stage patients (a minority of FL patients, 15-30%), FL is not curable with standard therapy. The great majority of FL patients will either have relapse after an initial response/remission to upfront chemo-immunotherapy or a minority of patients will have refractory disease. Although FL is often responsive to subsequent treatments, agents used in the second-line and beyond typically lead to shorter remissions.[23] Although hematopoietic stem cell transplantation (HSCT) can be utilized in patients with rel/ref FL to prolong remission duration and potentially provide durable responses and cures, there are significant toxicities associated with transplantation and many FL patients are not eligible for HSCT due to co-morbidities or age.[32-36] Effective novel, targeted therapies that have favorable toxicity profiles are urgently needed for patients with FL.

4.1.3 Classical Hodgkin Lymphoma

Classical HL is a lymphoma of B-cell origin that is defined by the presence of Hodgkin-Reed-Sternberg cells in a background of inflammatory cells. HL accounts for about 10% of all lymphomas, with approximately 9,000 new cases in the United States in 2013 and 1,200 deaths.[1] Although the majority of patients with HL are cured with upfront therapy, as many as 20-40% of patients will have relapsed or refractory disease.[37, 38] Similar to DLBCL, standard of care treatment for patients with rel/ref HL is salvage chemotherapy followed by ASCT in chemosensitive patients, and about half of HL patients who undergo ASCT will relapse.[39, 40] HL patients who are refractory to second-line therapy or relapse after ASCT have poor outcomes.[41] Therefore, improved therapies for patients with rel/ref HL are urgently needed.

4.2 PD-1/PD-L1 Pathway and PD-1/PD-L1 Inhibition in Lymphoma

The programmed death receptor-1 (PD-1) pathway is an immune checkpoint that normally serves to dampen immune responses in tissues. PD-1 is expressed on activated T-cells and binds its ligands, PD-L1 and PD-L2, on tissue cells or antigen presenting cells to decrease T-cell activation, proliferation, and survival.[6] Tumor cells can co-opt this pathway to evade attack by the host immune system.[6] A wide range of hematologic malignancies express PD-1 or PD-L1, including Hodgkin's lymphoma (HL),[7] diffuse large B-cell lymphoma (DLBCL),[8] primary mediastinal B-cell lymphoma (PMBCL),[7, 42] follicular lymphoma (FL),[9] chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL),[43] peripheral T-cell lymphomas (PTCL),[44-48] multiple myeloma (MM),[49] acute myelogenous leukemia (AML),[50, 51] and myelodysplastic syndrome (MDS).[52, 53] In addition, molecular analyses have demonstrated that genetic alterations involving PD-L1 and its overexpression are critical in the pathogenesis of

HL, PMBCL, and Epstein-Barr virus-associated post-transplant lymphoproliferative disorders.[7, 10]

Inhibitors of PD-1 and PD-L1 have produced clinical responses in early-phase studies in patients with a range of lymphomas, including HL, DLBCL, and FL. Pidilizumab (CureTech, Yavne, Israel) produced responses as a single-agent in patients with rel/ref FL, CLL, and HL, in a phase I study,[11] and yielded a 66% ORR when used in combination with rituximab in patients with relapsed or refractory FL in a phase II study.[12] A phase Ib study of nivolumab demonstrated an 87% overall response rate (ORR) and 100% clinical benefit rate in 23 patients with relapsed or refractory HL.[14] A subsequent phase II study of nivolumab in 80 patients who failed ASCT as well as prior brentuximab vedotin confirmed a high ORR of 66%, with 9% of patients having a complete response per independent review. Notably, the majority of responders remained in remission at the time of censoring, thus a significant proportion of responses appear to be durable.[54] A phase Ib study of pembrolizumab in 31 patients with rel/ref HL who failed prior brentuximab vedotin demonstrated a 65% ORR with 16% of patients achieving CR.[55] A phase II study of pembrolizumab in patients with rel/ref HL is ongoing, but interim reports have demonstrated an ORR of 70%.[56] Similarly, in a phase Ib study of nivolumab, a 36% ORR was observed in patients with rel/ref DLBCL, and a 40% ORR was observed in patients with rel/ref FL.[57] In an early interim analysis, the PD-L1 inhibitor, atezolizumab, in combination with obinutuzumab produced a 15% ORR in patients with rel/ref DLBCL or FL.

4.3 Histone Deacetylase Inhibition and Vorinostat In Lymphoma

Histone deacetylases (HDAC) are important epigenetic regulators of gene expression, modulating many cellular functions including cell proliferation and survival. They induce deacetylation of histones, the core proteins around which the nucleic acids are wound, keeping them in tight coils, thus silencing gene expression, including genes involved with cell differentiation, survival, and apoptosis. HDAC inhibitors (HDACi) render the DNA more open for transcription, resulting in increased expression of several genes that are often silenced in cancer, such as tumor suppressor genes.

HDACis, including vorinostat, have been evaluated in a range of malignancies, including lymphoma and other hematologic malignancies. In a phase I study of vorinostat in hematologic malignancies, several patients with rel/ref lymphomas exhibited anti-tumor responses, including 4 patients with HL and 3 patients with DLBCL (including 2 with transformed DLBCL).[16] Phase II studies of vorinostat in DLBCL and HL only produced ORR of 5.6% and 4% respectively, however, a significant proportion of patients in the HL study (48%) had stable disease (SD) and 7 HL patients remained progression-free for over a year.[17, 58] Panobinostat is another HDACi that has been evaluated in the treatment of HL, producing a 27% ORR in a phase II study of rel/ref patients with relapse after ASCT.[59] The ORR to single agent vorinostat in patients with rel/ref FL is 47-49%, with a long median DOR of 27 months in responders. Vorinostat has also been evaluated in combination with rituximab for the treatment of FL, resulting in an ORR of 46%, including 67% for previously untreated patients and 41% for rel/ref patients.[18]

Vorinostat and other HDACis have been studied extensively in the treatment of cutaneous T-cell lymphomas (CTCL) and peripheral T-cell lymphomas (PTCL). Romidepsin is an HDACi that has been approved for the treatment of PTCL and CTCL. Of the 131 patients enrolled in the pivotal phase II trial, 130 had histologically confirmed PTCL by central review. The objective response rate was 25% (33 of 130), including 15% (19 of 130) with CR/CRu. The median duration of response was 17 months, with the longest response ongoing at 34+ months. Of the 19 patients who achieved CR/CRu, 17 (89%) had not experienced disease progression at a median follow-up of 13.4 months.[60] Belinostat is a pan-HDAC inhibitor that was evaluated in an open-label phase II study. A total of 129 relapsed/refractory PTCL patients received 1000 mg/m^2 belinostat infusion on days 1–5 of every 3-week cycle. Among 120 evaluable patients, the ORR was 26%, including 10% CR, and median response duration was 8.3 months.[61]

4.4 Study Agent: Pembrolizumab (MK-3475)

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

4.4.1 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. It is designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the anti-tumor immune response. Keytruda™ (pembrolizumab) has recently been approved in the United Stated for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor.

4.4.2 Nonclinical Pharmacology

Pembrolizumab strongly enhances T lymphocyte immune responses in cultured blood cells from healthy human donors, cancer subjects, and primates. In T-cell activation assays using human donor blood cells, the EC50 has been 0.1 to 0.3 nM. In addition to interleukin-2 (IL-2), tumor necrosis factor alpha (TNFα), interferon gamma (IFNγ), and levels of other cytokines were found to be modulated by pembrolizumab. The antibody potentiates existing immune responses only in the presence of antigen and does not non-specifically activate T cells. Using an anti-murine PD-1 analog antibody, PD-1 blockade has been shown to significantly inhibit tumor growth in a variety of syngeneic murine tumor models.

4.4.3 Nonclinical Pharmacokinetics

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

4.4.4 Preclinical Safety

The potential for systemic toxicity of pembrolizumab was assessed in a 1-month repeat-dose toxicity study with a 4-month recovery in cynomolgus monkeys and in a 6-month repeat- dose toxicity study with a 4-month recovery period in cynomolgus monkeys. In the 1- month toxicity study, cynomolgus monkeys were administered an IV dose of 6, 40, or 200 mg/kg once weekly for a total of five doses. Four monkeys per sex per group were euthanized during Week 5. The remaining two monkeys/sex/group were euthanized during Week 23, after a four-month post-dose period. In this study, pembrolizumab was well- tolerated in monkeys with the systemic exposure (AUC) up to approximately 170,000 μg/day/mL over the course of the study. There was no test article-related mortality, and test article-related changes were limited to an increased incidence of inguinal swelling, and increased splenic weights in males receiving 200 mg/kg. Both of these findings were not considered adverse and there was no histopathologic correlation. Splenic weights were normal at the post-dose necropsy. Anti-pembrolizumab antibodies were detected in seven (out of eight) animals in the 6 mg/kg dose group and one (out of eight) animal in the 40 mg/kg dose group, and were associated with an apparent increase in clearance of pembrolizumab. The presence of anti-drug antibodies (ADA) in monkeys in the low-dose group and in one monkey in the mid-dose group did not impact the pharmacodynamic response as sufficient target engagement was demonstrated for the duration of the study (with the exception of one low-dose monkey). Additionally, anti-pembrolizumab antibodies were not detected in any monkeys in the high-dose group, suggesting that potential toxicity has been evaluated at the highest exposure levels in the study. Based on the lack of adverse test article-related findings in this study, the No Observable Adverse Effect Level (NOAEL) was ≥200 mg/kg. In the 6-month toxicity study, the potential for systemic toxicity was assessed in cynomolgus monkeys administered an IV dose of 6, 40, or 200 mg/kg once every other week for approximately 6 months (a total of 12 doses) followed by a 4-month treatment-free period. Three animals/sex/group were designated for interim necropsy at the end of the 6-month dosing phase (3 days after receiving the last dose in Study Week 23); and the remaining monkeys were designated for final necropsy following the 4-month treatment-free period. Pembrolizumab was well tolerated at all dose levels. There were no test article-related antemortem findings. There were no test article-related electrocardiographic or ophthalmic findings. There were no test article-related changes at injection sites. There were no test article-related gross observations or organ weight changes at the interim or final necropsy. Since there were no test article-related histomorphologic findings at interim necropsy, histomorphologic evaluation of tissues collected at final necropsy was not conducted. The presence of ADA was observed in five out of ten animals at 6 mg/kg/dose during the dosing phase, which correlated with an apparent increased rate of elimination of pembrolizumab in these animals. No anti-pembrolizumab antibodies were detected at 40 or 200 mg/kg/dose during the dosing phase, and no pembrolizumab serum concentration profiles in these two groups suggested an effect of ADA on pembrolizumab elimination rate. During the treatment-free period, anti-pembrolizumab antibodies were detected in two animals at 6 mg/kg/dose, which already had ADA present during the dosing phase, and in two additional animals (one at 6 mg/kg/dose and one at 200 mg/kg/dose), which were ADA negative during the dosing phase. The detection of anti-pembrolizumab antibodies

had a minimal effect on the mean group systemic exposure to pembrolizumab during the study and did not impact the evaluation of potential toxicity of pembrolizumab for the duration of the 6-month study as there were no test article-related effects on any of the parameters examined and as no monkey in the mid- and high-dose groups developed ADA during the dosing phase. In conclusion, pembrolizumab administered once every other week over a 6-month duration to cynomolgus monkeys was well tolerated and the no observed effect level (NOEL) was ≥200 mg/kg/dose (the highest dose tested).

In addition, tissue cross-reactivity studies using monkey and human specimens were conducted to evaluate the potential cross reactivity of pembrolizumab with cryosections of cynomolgus monkey tissues and normal human tissues. Results demonstrated the expected on-target staining of the membranes of mononuclear leukocytes in both species. The off-target staining (cytoplasmic and stromal) that occurred in many tissues of both species was considered spurious binding inherent to the experimental conditions of the in vitro tissue cross reactivity studies with no in vivo toxicological significance.

4.4.5 Clinical Safety

Several ongoing studies are testing the anti-tumor activity of pembrolizumab. Protocol 001 (PN001), an open-label Phase I study is being conducted to evaluate the safety and clinical activity of pembrolizumab when administered as monotherapy. The dose escalation portion of this study evaluated three dose levels of single agent pembrolizumab (1 mg/kg, 3 mg/kg, and 10 mg/kg), in subjects with advanced solid tumors. All three dose levels were well tolerated and no dose-limiting toxicities (DLTs) were observed, therefore the maximum tolerated dose (MTD) has not been determined. The ongoing expansion part of this study is evaluating pembrolizumab in subjects with melanoma and non-small cell lung cancer (NSCLC). Protocol 002 (PN002), a Phase II study, is also being conducted to evaluate the safety and clinical activity of pembrolizumab in melanoma. This study is examining two dose levels of pembrolizumab (2 mg/kg and 10 mg/kg) in subjects with metastatic melanoma. Due to the limited amount of safety data for this compound a well-defined safety profile has not been established, however immune-related adverse events (irAEs) are expected based on the nature of the compound, its mechanism of action and reported experience with immunotherapies that have a similar mechanism of action. Protocol 013 is a Phase 1b study testing pembrolizumab at a fixed dose of 10 mg/kg every 2 weeks in patients with myelodysplastic syndromes, cHL, PD-L1-positive non-Hodgkin lymphoma, and multiple myeloma. This study is ongoing.

In the pembrolizumab monotherapy trials (P001/P002, P012, P013, and P028, plus the P011 monotherapy arm), the overall incidence of AEs ranged from 83.0% (73 of 88 subjects in P012) to 100% (10 of 10 subjects in P011). The most commonly reported AEs included fatigue, diarrhea, decreased appetite, nausea, and anemia. The incidence of drug-related AEs (DRAEs) ranged from 39.8% (35 of 88 subjects in P013) to 80.0% (8 of 10 subjects in P011). The most commonly reported DRAEs across all studies were nausea, fatigue, and diarrhea. The incidence of Grade 3-5 DRAEs across studies ranged from 6.8% (6 of 88 in P013) to 12.0% (187 of 1562 subjects) in P001/P002. The most commonly reported Grade 3-5 DRAEs were

anemia, alanine aminotransferase increased, and aspartate aminotransferase increased. Most subjects who experienced an AE continued in the study, with the incidence of AEs leading to discontinuation ranging from 1.9% (8 of 430 subjects in P028) to 12.3% (192 of 1562 subjects in P001/P002). The majority of AEs leading to discontinuation were not considered drug-related. Discontinuations due to a DRAE were infrequent and ranged from 0% (no subjects in P011) to 4.5% (4 of 88 subjects in P013). The most commonly reported DRAEs leading to discontinuation were pneumonitis, alanine aminotransferase increased, and aspartate aminotransferase increased.

The overall pattern of AEs observed in melanoma subjects enrolled in P002 demonstrates favorable safety profile when this immune therapy is compared to chemotherapy. Consistent with prior observations from randomized comparisons of the 2 mg/kg and 10 mg/kg dose levels when given every 3 weeks, there are no important differences in the safety profile of pembrolizumab at these 2 dose levels, and both doses appear to have a favorable safety profile compared to chemotherapy.

In the pembrolizumab monotherapy trials, the most commonly reported drug-related serious adverse events (DRSAEs) (those that occurred in 3 or more subjects overall in at least 1 study) were pneumonitis (range of 0.7% to 1.3% of subjects); colitis (range of 0.3% to 0.9% of subjects), pyrexia (range of 0.3% to 0.5% of subjects); diarrhea (range of 0.2% to 0.4%); hepatitis (0.7% of subjects); nausea, adrenal insufficiency, hyponatraemia, hyperthyroidism, hypophysitis, vomiting, and dyspnea (0.3% of subjects each); and dehydration, generalised edema, hypothyroidism, renal failure acute, and pericardial effusion (0.2% of subjects each). The remaining DRSAEs occurred in 1 or 2 subjects each per study.

Among P001 and P002 studies, the incidence of adverse events of special interest (AEOSI) was 16.1%. Overall, the most commonly reported AEOSI included hypothyroidism (7.2% of subjects), pneumonitis (2.9% of subjects), infusion reaction (2.5% of subjects), and hyperthyroidism (2.2% of subjects). The incidences of the remaining AEOSI were low (range of 0.1 to 1.3% of subjects). The overall incidence of drug-related AEOSI was 14.3%. Overall, 2.6% of subjects discontinued treatment due to an AEOSI and the most commonly reported drug-related AEOSI leading to discontinuation was pneumonitis (1.3% of subjects). Only one subject died of AEOSI (pneumonitis, 0.1% of subjects). No corticosteroids were used to manage myositis, pericarditis, thyroiditis, type 1 diabetes mellitus, uveitis and vasculitis.

For additional information on the study agent, please refer to the Investigator's Brochure.

4.4.6 Expected Adverse Events

Per the IB, the expected toxicities for pembrolizumab are as follows (asterisk signifies ≥ 10%; no asterisk signifies 1-10%, † signifies < 1%, and ^ signifies unknown frequency):

Blood and lymphatic system disorders (includes investigations)	Anemia, neutropenia†, thrombocytopenia†, leukopenia†, lymphopenia†, eosinophilia†, hemolytic anemia†,immune thrombocytopenic purpura†
Cardiac	Myocarditis†
Endocrine	Hyperthyroidism, hypothyroidism, hypophysitis †, adrenal insufficiency †, thyroiditis†
Eye	Uveitis †, dry eye †, Vogt-Koyanagi-Harada disease ^
Gastrointestinal	Diarrhea*, nausea *, abdominal pain, vomiting, colitis, constipation, dry mouth, pancreatitis †, small intestine perforation †
General Disorders and Administration Site	Fatigue *, asthenia, edema, pyrexia, influenza-like illness, chills
Hepatobiliary	Hepatitis†
Immune system	Infusion related reactions, severe infusion reactions †, sarcoidosis †, solid organ transplant rejection ^, GvHD (potential risk), haemophagocytic lymphohistiocytosis †
Investigations (excluding hematologic)	AST/ALT increased, blood alkaline phosphatase increased, blood creatinine increased, low sodium levels†, low potassium levels†, low calcium levels†, blood bilirubin increased†, amylase increased†, increased calcium†
Metabolism and Nutrition	Decreased appetite, type 1 diabetes mellitus †
Musculoskeletal and Connective Tissue	Arthralgia, back pain, myositis, musculoskeletal pain, arthritis, pain in extremity, tenosynovitis †
Nervous system	Headache, dizziness, dysgeusia, epilepsy†, lethargy†, Guillian-Barré syndrome†, peripheral neuropathy†, myasthenic syndrome†, encephalitis†, myelitis†
Psychiatric disorders	Insomnia †
Renal and urinary	Nephritis †
Respiratory, Thoracic and Mediastinal	Cough, pneumonitis, dyspnoea
Skin and Subcutaneous Tissue	Pruritus*, rash*, vitiligo, dry skin, erythema, hair color change †, eczema †, alopecia †, severe skin reactions†, Steven-Johnson Syndrome†, toxic epidermal necrolysis†
Vascular Disorders	Hypertension †

4.4.7 Immune-Related Adverse Events

An irAE is defined as a clinically significant AE of any organ that is associated with study drug exposure, is of unknown etiology, and is consistent with an immune-related mechanism. AEOSI data for melanoma and lung subjects demonstrates that irAEs were reported in 16.1% of subjects (251 of 1562) overall; AEOSI were considered by the Investigators to be drug related in 14.3% of subjects (223 of 1562). The majority of AEOSI were Grade 1 or 2 in

severity. Overall, serious AEOSI occurred in 4.2% of subjects at 2 mg/kg Q3W, 3.7% of subjects at 10 mg/kg Q3W, and 3.9% of subjects at 10 mg/kg Q2W. There was one AEOSI (pneumonitis) related to death in 10 mg/kg Q3W arm, in a subject with NSCLC. The rate of discontinuation due to AEOSI was low (2.6%).

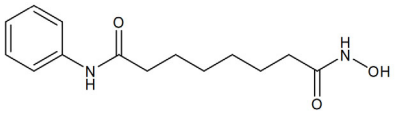
The most commonly reported immune-related adverse events across the dose schedules are hypothyroidism (7.2%), pneumonitis (2.9%), hyperthyroidism (2.2%), colitis (1.3%) and skin AEOSI (1.3% including all terms). Based on the mechanism of action of MK-3475 and similar immunomodulatory agents, Merck is interested in potential irAEs, and encourages appropriate investigation of signs and symptoms suggestive of these. Consultation with the appropriate medical specialist should be considered when investigating a possible irAE. These events can occur after the first dose to several months after the last dose of treatment. Mild irAEs are usually treated symptomatically and do not require dosing delays or discontinuation. Higher grade and persistent lower grade irAEs typically necessitate withholding or discontinuing treatment and administration of systemic steroids or other immunosuppressive agents (such as tumor necrosis factor blockers), when systemic steroids are not effective. Early recognition of irAEs and initiation of treatment are critical to reduce the risk of complications, since the majority of irAEs are reversible with the use of steroids and other immune suppressants.

4.5 Study Agent: Vorinostat

Histone deacetylase (HDAC) inhibitors are a novel class of anti-cancer agents that act by regulating chromatin structure and function[24]. HDACis induce acetylation of histones, the core proteins around which the nucleic acids are wound. The HDACis exert their targeted action during post-translational acetylation of core nucleosomal histones, which affects chromatin structure, thereby regulating gene expression. DNA that is wrapped around condensed, non-acetylated histones is transcriptionally inactive, whereas acetylation of N-terminal histone lysine residue exposes DNA to important transcription factors that promote transcriptional activity.[62, 63] The dynamic equilibrium between histone acetylation and deacetylation is regulated by histone acetyltransferases (HATs) and HDACs. The action of HDACs on nucleosomal histones leads to tight coiling of chromatin and silencing of expression of various genes, including those implicated in the regulation of cell survival, proliferation, differentiation and apoptosis. [64] The effects of HDACs are not limited to histone deacetylation. HDACs also act as members of a protein complex to recruit transcription factors to the promoter region of genes, including those of tumor suppressors, and they affect the acetylation status of specific cell cycle regulatory proteins.[65]

Acetylation of regulatory proteins such as heat shock protein 90, hypoxia-inducing factor alpha and alpha tubulin, may also contribute to the anti-cancer effects of HDAC inhibitors.[66-69] These molecular events ultimately result in induction of apoptosis, cell cycle arrest, modulation of anti-cancer immunity and inhibition of angiogenesis.[67, 70-73]

Vorinostat is described chemically as *N*-hydroxy-*N′*-phenyloctanediamide. The empirical formula is $C_{14}H_{20}N_2O_3$. The molecular weight is 264.32 and the structural formula is:



Vorinostat is a hydroxamic acid derivative that inhibits class I and II HDACs. It has been approved by the United States Food and Drug Administration (FDA) for the treatment of patients with cutaneous T-cell lymphoma at a dose of 400mg by mouth once daily.[74] It is administered orally on either a continuous daily or intermittent schedule. The common adverse effects of vorinostat include nausea, emesis, fatigue and thrombocytopenia.[65]

4.5.1 Pharmacology

Vorinostat, the drug form of the compound suberoylanilide hydroxamic acid (SAHA, or MK-0683), is a novel agent that inhibits the enzymatic activity of histone deacetylases (HDACs). Vorinostat is a potent inhibitor of HDAC activity and binds directly to the catalytic pocket of Class I and II HDAC enzymes. Vorinostat inhibits the enzymatic activity of both Class I (HDAC1, 2 and 3) and Class II (HDAC6) HDACs at low nanomolar concentrations (IC50<86 nM). The anti-neoplastic effect of vorinostat is attributed to the inhibition of HDAC activity and subsequent accumulation of acetylated proteins, including the core nucleosomal histones. This accumulation influences the regulation of gene expression. Exposure to vorinostat led to G1 or G2 phase cell-cycle arrest, apoptosis, or differentiation in cultured transformed cells. The growth inhibitory activity of vorinostat was demonstrated on the 60 cell line screen at National Cancer Institute (NCI), with IC50s ranging from approximately 38.6 nM to 6.2 μM. Additionally, vorinostat demonstrated synergistic and additive activity in combination with other cancer therapies (including radiation, kinase inhibitors, cytotoxic agents, and differentiating agents) in a variety of cultured human transformed cell lines.

The pharmacokinetics and toxicokinetics of vorinostat have been evaluated in mice, rats, dogs and humans. Rapid oral absorption has been noted in all species studied. Vorinostat (0.5 to 50 μg/mL) exhibited moderate reversible binding to plasma proteins. In human plasma, vorinostat appears to bind primarily to human serum albumin; however, some binding of vorinostat was also observed in solutions of human α1-acid glycoprotein.

Vorinostat is excreted exclusively as metabolites, the majority of metabolites are derived from glucuronidation and hydrolysis with β-oxidation pathway metabolites accounting for the rest. As vorinostat is not eliminated via cytochrome P450 pathways, it is anticipated that vorinostat will not be subject to drug-drug interactions when co-administered with drugs that are known to be CYP inhibitors. Although vorinostat was not a potent reversible inhibitor of the cytochrome P450 isozymes (IC50 >75 μM), gene expression studies detected some potential for suppression of CYP2C9 and CYP3A4 activities at ≥10 μM vorinostat however,
these changes were observed at concentrations higher than the pharmacologically relevant serum concentration of 2 μM (Cmax).

4.5.2 Toxicology

The main toxicities observed in *in vivo* animal models were weight loss and inappetence, anemia (rats only at 3.6 times the equivalent 400 mg human dose), leukopenia (rats only at 1.3 times the equivalent 400 mg human dose), thrombocytopenia (male rats only, statistically significant change at 0.5 times the equivalent 400 mg human dose but within normal range at all doses), and gastrointestinal tract irritation (dogs only, at 8.5 times the equivalent 400 mg human dose). Although statistically significant and dose-dependent, many of the clinical pathology findings were within normal historical ranges indicating that they should not have major toxicological consequences. The toxicities appeared to be rapidly reversible within 12 to 14 days. There has been no evidence of cardiac toxicity based on electrocardiogram (ECG, dogs only), blood pressure (dogs only), heart rate (dogs only), creatinine kinase, organ weight, gross pathology, or histopathology assessments in studies up to one month duration. No serious, irreversible damage to any vital organ has been observed. Importantly, toxicities in rats and dogs were predictive of adverse effects in humans (thrombocytopenia, anaemia, nausea, diarrhea, fatigue). Toxicities present in animals would be manageable in the clinic, and the onset of serious toxicity is readily forecast by prodromal symptoms. The nonclinical toxicity profile of vorinostat is acceptable for an oncology drug.

Vorinostat was evaluated in a panel of genetic toxicity assays; in vivo and in vitro assays were found to be positive. Therefore, vorinostat should not be taken by pregnant women. Pregnancy should be avoided both in female subjects taking vorinostat, and in female partners of male subjects taking vorinostat for at least 30 days after last dose of vorinostat, as data are not yet available to establish the safety of vorinostat ingestion in male patients who impregnate their partners.

4.5.3 Biological Activity of Vorinostat

Vorinostat was identified originally by its ability to induce differentiation of murine erythroleukemia cells at micromolar concentrations.[75, 76] Subsequently, it was found to induce differentiation or arrest growth of a wide variety of human carcinoma cells. To date, vorinostat activity has been reported in transformed hematopoietic cells, such as a multiple myeloma (MM),[77] acute promyelocytic leukemia (APL),[78] acute lymphocytic leukemia (ALL), chronic myelogenous leukemia (CML),[79] Waldenstrom's macroglobulinemia,[80] and cutaneous T-cell lymphoma (CTCL).[81] Activity has also been reported in cell lines representing other tumor types including bladder transitional cell carcinoma,[82] breast cancer,[83] prostate cancer,[84] head and neck squamous cell carcinoma, and colon carcinoma.[85]

Vorinostat has demonstrated biological and anti-neoplastic activity in xenograft models of human carcinomas. Intraperitoneal administration of vorinostat (up to 100 mg/kg/day) caused significant inhibition of tumor growth in human cutaneous T-cell lymphoma (CTCL), prostate cancer, human breast cancer, and human colon cancer xenografts in mice without toxic side effects. Some tumor regression was even noted. Oral vorinostat also inhibited growth of established rat mammary tumors. Additionally, oral vorinostat administered to carcinogen-treated rats increased tumor latency and reduced mammary tumor incidence, multiplicity, and

volume. Oral vorinostat administered to carcinogen-treated mice reduced lung tumor multiplicity. In addition, the intraperitoneal administration of vorinostat in combination with retinoic acid induced leukemic remission and prolonged survival in a therapy-resistant transgenic mouse model of acute promyelocytic leukemia (APL).[86] Furthermore, administration of vorinostat in combination with bortezomib significantly inhibited tumor growth compared to either agent alone using the orthotopic model of human pancreatic cancer. The combination of vorinostat with bortezomib was well tolerated. These data show that significant anti-tumor activity can be achieved in these nonclinical models at easily-tolerated vorinostat doses.

4.5.4 Summary of Clinical Data

As of 02-Jul-2012 the clinical safety of vorinostat is supported by data from 1,740 patients (1,744 patient-exposures) who have been treated in Merck-sponsored Phase I, II, and III studies (PN001, PN002, PN003, PN004, PN005, PN006, PN008, PN011, PN012, PN013, PN014, PN015, PN016, PN025, PN029, PN030, PN042, PN048, PN055, PN056, PN058, PN064, PN066, PN070, PN074, PN088, PN089, PN095, PN098, and PN103) conducted in patients with both hematologic malignancies and solid tumors. (The additional four (4) patient-exposures occurred in PN005, the initial supportive study, where patients enrolled in 1 cohort were permitted to enroll in a subsequent cohort at a later time point). Merck, including MSD KK (Japan), has sponsored 30 vorinostat studies that are completed (24), closed (3), or ongoing (3). Three (3) Merck-sponsored studies (PN016, PN056, and PN064) were terminated.

The NCI is working in collaboration with Merck to further evaluate vorinostat. The NCI-sponsored studies of vorinostat are in progress or are planned in a variety of different indications both in hematologic malignancies as well as solid tumors. As of 02-Jul-2012, 1,718 patients have received vorinostat as either monotherapy or combination chemotherapy in 61 studies sponsored by the NCI. A separate U.S. Investigational New Drug application (IND) is held by NCI for these studies.

In addition, vorinostat is also being evaluated in studies initiated and sponsored by independent Investigators (MISP studies), both as monotherapy and as combination chemotherapy. As of 02-Jul-2012, 85 of these MISP studies have enrolled 1,607 patients. These active studies are enrolling and additional studies are planned. Merck has outsourced the management, including data collection, of 4 clinical trials involving vorinostat and radiation to the NCCN. As of 02-Jul-2012, all 4 of these studies were opened and had enrolled a total of 31 patients. Data from these 31 patients are reported separately. A separate U.S. Investigational New Drug application (IND) is held by the NCCN investigators for these studies. Therefore, over 5,000 patients have received at least one dose of vorinostat in studies sponsored by either Merck, the NCI, NCCN, or independent Investigators. ZOLINZA™ (vorinostat) was approved by the U.S. Food and Drug Administration (FDA) on 6-Oct-2006 for the treatment of cutaneous manifestations in patients with cutaneous T-cell lymphoma (CTCL) who have progressive, persistent or recurrent disease on or following two systemic therapies. ZOLINZA™ (vorinostat) has been approved in several other markets around the world for this indication as well.

4.5.5 Safety

The total daily doses studied ranges from 200 mg to 900 mg. The tolerability of oral vorinostat appears to be determined by total daily dose and the length of consecutive days of dosing. The maximum tolerated dose (MTD) for continuous daily dosing without a rest period is 400 mg daily or 200 mg BID. The MTD for intermittent dosing is 300 mg BID x 3 consecutive days per week, or 250 mg TID x 14 consecutive days followed by a 7-day rest. Dose-limiting toxicities (DLTs) of single agent vorinostat were mainly non-hematologic (anorexia, dehydration, diarrhea, and fatigue); hematologic toxicities are primarily anemia and thrombocytopenia, most of which were mild to moderate. The majority of these DLTs occurred within the first month on oral vorinostat. The DLTs were manageable because these toxicities resolved quickly after drug administration was interrupted. The optimal dose, dose frequency, and dose duration remain under active investigation.

4.5.6 Expected Adverse Events

The types of adverse experiences observed in clinical trials of vorinostat were those usually associated with chemotherapy, such as nausea, fatigue, diarrhea, anorexia, vomiting, constipation and cytopenias. The three major clinical categories of adverse experiences attributable to vorinostat include a constellation of gastrointestinal symptoms, constitutional complaints, and cytopenias. However, most of the adverse experiences were manageable. In fact, most of the very common adverse experiences were reversible and could be managed using conventional supportive care for chemotherapy. On the whole, treatment with oral vorinostat was well tolerated for use in the outpatient setting. Please see below for specific information regarding vorinostat-related adverse experiences observed when vorinostat was administered either as monotherapy or in combination with other agents, in Merck-sponsored clinical trials.

Nausea and Vomiting
Drug-related nausea and vomiting are commonly observed with vorinostat therapy: 51.3% all grades nausea, 4.9% grades 3-5 nausea; 32.5% all grades vomiting, 3.2% grades 3-5 nausea. Nausea and vomiting should be managed according to standard practice as outlined in the published American Society of Clinical Oncology (ASCO) antiemetic guidelines. Briefly, antiemetic agents including, but not limited to, 5HT-3 antagonists, aprepitant, lorazepam, diphenhydramine or phenothiazines may be considered. The use of empiric anti-emetic coverage is strongly encouraged, as is early and aggressive management of nausea, decreased oral intake and/or vomiting in patients treated with vorinostat.

Diarrhea
Drug-related diarrhea is commonly with vorinostat therapy: 43.5% all grades diarrhea, 6.7% grades 3-5 diarrhea. Diarrhea should be treated promptly with appropriate supportive care. Patients should be instructed to begin taking loperamide at the first sign of: 1) poorly formed or loose stool, 2) occurrence of more bowel movements than usual in one day or 3) unusually high volume of stool. Diarrhea should be managed with loperamide or according to institutional guidelines. However, loperamide should be deferred if blood or mucus is present

in the stool or if diarrhea is accompanied by fever. In this setting, appropriate diagnostic microbiologic specimens should be obtained to exclude an infectious etiology. Patients should also be advised to drink liberal quantities (at least 2 liters/day) of clear fluids to help prevent dehydration.

Dehydration
Altered taste and decreased food and liquid intake are associated with vorinostat administration. These toxicities can be actively managed with fluid management and nutritional consultation, as appropriate. To prevent dehydration, patients should consume at least 2 liters of fluid orally, on a daily basis, in particular during the days that patients are being treated with vorinostat. If patients are experiencing dysgeusia, popsicles or oral electrolyte fluid replacement may be recommended.

Anemia
Treatment with vorinostat can cause dose-related anemia which may result in fatigue, lethargy or shortness of breath. If hemoglobin is reduced during treatment with vorinostat, the dose should be modified or therapy discontinued, as outlined in the respective protocol.

Neutropenia
Drug-related neutropenia is observed with vorinostat therapy, 17.8% all grades neutropenia, 13.3% grades 3-5 neutropenia. Growth factors should only be utilized according to protocol guidelines.

Thrombocytopenia
Treatment with vorinostat can cause dose-related thrombocytopenia. Transfusion of platelets may be used if clinically indicated in a manner consistent with the guidelines for dose modification as outlined in the respective protocol.

Hyperglycemia
Hyperglycemia has been observed in patients receiving vorinostat. Serum glucose should be monitored, especially in diabetic or potentially diabetic patients. Adjustment of diet and/or therapy for increased glucose may be necessary.

Hypokalemia or Hypomagnesemia
Hypokalemia and hypomagnesemia should be corrected prior to administration of vorinostat, and consideration should be given to monitoring potassium and magnesium in symptomatic patients (e.g., patients with nausea, vomiting, diarrhea, fluid imbalance or cardiac symptoms.)

Pulmonary Embolism
Among the 1,740 patients enrolled in Merck-sponsored studies, pulmonary embolism and deep vein thrombosis have been reported in 30 (1.7%) and 32 (1.8%) patients, respectively. Investigators should be alert to the signs and symptoms of PE and DVT, particularly in patients with a prior history of thromboembolic experiences.

QTc Prolongation
QTc prolongation has been observed in patients receiving vorinostat although no statistical correlation has been established between the use of vorinostat and QTc prolongation. If clinically indicated or outlined in the respective study, baseline and periodic ECGs should be performed during treatment. Vorinostat should be administered with particular caution in patients with congenital long QT-syndrome and patients taking anti-arrhythmic medicines or other medicinal products that lead to QT prolongation.

4.5.7 Drug Interactions

The major pathways of metabolism of vorinostat involve glucuronidation and β-oxidation. As vorinostat is not eliminated via CYP450 pathways, it is anticipated that vorinostat will not to be subject to drug-drug interactions when co-administered with drugs that are known to be CYP450 inhibitors. Although vorinostat was not a potent reversible inhibitor of the CYP450 isozymes, studies performed to monitor gene expression changes indicated some potential for suppression of CYP2C9 and CYP3A4 activities at ≥10 μM vorinostat; however, these changes were observed at concentrations higher than the pharmacologically relevant concentration of 2 μM (Cmax).

Prolongation of prothrombin time (PT) and International Normalized Ration (INR) have been observed in patients receiving vorinostat concomitantly with coumarin-derivative anticoagulants. Physicians should carefully monitor PT and INR in patients concurrently administered vorinostat and coumarin derivatives. Vorinostat should not be administrated with other HDAC inhibitors (e.g., valproic acid) as class-specific adverse reactions may be additive. Severe (grade 4) thrombocytopenia with associated gastrointestinal bleeding and anemia has been reported with the concomitant use of vorinostat and valproic acid.

4.6 Rationale

4.6.1 Rationale for the Trial and Selected Subject Population

Although responses to PD-1 inhibitors have been observed in patients with HL, DLBCL, and FL, there is room for improvement. Despite the high response rate observed to single-agent PD-1 inhibition, the complete response (CR) rate in patients with HL appears to be only 10-20%.[14] Meanwhile, the ORR and CR rate are only 35-40% and 5-10% in patients with DLBCL or FL, respectively.[15] The addition of a synergistic agent with PD-1 inhibition may enhance anti-tumor activity and result in deeper and more durable responses. An attractive combination partner is vorinostat, a histone deacetylase inhibitor (HDACi), which has demonstrated activity in a range of lymphomas, including HL, DLBCL, and FL.[16, 17 18-21]

HDACi therapy has many immunologic effects on tumor cells and immune effector cells that may enhance the effect of PD-1 blockade when given in combination. HDACis immunomodulate tumor cells, by increasing expression of tumor-associated antigens, upregulating genes that control antigen presentation machinery, and promoting release of mediators of immunogenic cell death.[22] HDACis also have important effects on immune cells,

including enhancing CD8+ cytotoxic T-lymphocyte (CTL) function, decreasing regulatory T-cell numbers and function, and modulating myeloid-derived suppressor cell (MDSC) differentiation.[22] Most notably, **there is evidence that HDAC inhibition combined with PD-1/PD-L1 pathway blockade results in enhanced anti-tumor activity in preclinical models.** HDACis directly upregulate PD-L1 expression in melanoma cell lines, murine models, and patient tumor samples.[23] Indeed, combined HDAC and PD-1 inhibition results in synergistic killing of tumor cells and HDACis reverse tumor resistance to checkpoint blockade in pre-clinical murine breast and colorectal cancer models.[24] Zheng et al. found that HDAC inhibition with romidepsin increases *in vitro* PD-L1 expression in lung cancer cell lines, promotes T-cell infiltration into lung cancers, and enhances function of recruited T-cells in a mouse model. In mice inoculated with lung cancer tumor cells, combined romidepsin and anti-PD-1 therapy significantly reduced tumor growth compared to HDAC or PD-1 inhibition alone.[25] The authors chose to study romidepsin based on a screen of drugs that could induce T-cell chemokine expression, but the authors also demonstrated in the study that vorinostat had similar effects. In a separate study using a murine model of lung cancer, vorinostat increased CD8+ T-cell infiltration into tumors.[26] In light of the observation that non-responders to anti-PD-1 therapy have a deficiency of tumor infiltrating T-cells in pre-treatment tumor biopsies,[27] the ability of vorinostat and HDACis to increase T-cell recruitment into tumors and to induce PD-L1 expression on tumor cells, as well as the ability of HDACis to synergize with anti-PD-1 therapy suggests that vorinostat may be an ideal agent to combine with a PD-1 inhibitor to increase the frequency and depth of responses in lymphoma patients. We will conduct a phase I study with an expansion cohort to evaluate the safety and obtain a preliminary estimate of the efficacy of combining pembrolizumab with vorinostat for the treatment of rel/ref HL, DLBCL, and FL.

4.6.2 Rationale for Pembrolizumab Dose Selection/Regimen/Modification

An open-label Phase I trial (Protocol 001) was conducted to evaluate the safety and clinical activity of single agent pembrolizumab (MK-3475). 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 MK-3475 showed evidence of target engagement and objective evidence of tumor size reduction at all dose levels (1 mg/kg, 3 mg/kg and 10 mg/kg Q2W). No MTD has been identified to date. Recent data from other clinical studies within the MK-3475 program has shown that a lower dose of MK-3475 and a less frequent schedule may be sufficient for target engagement and clinical activity.

PK data analysis of MK-3475 administered Q2W and Q3W showed slow systemic clearance, limited volume of distribution, and a long half-life (refer to IB). Pharmacodynamic (PD) data (IL-2 release assay) suggested that peripheral target engagement is durable (>21 days). This early PK and pharmacodynamic data provided 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 MK-3475 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. MK-3475 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 MK-3475 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.

2 mg/kg and comparable doses of pembrolizumab in solid tumors were further explored 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 for this study of the 200 mg Q3W, representing a 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.

4.6.3 Rationale for Vorinostat Dose Selection/Regimen/Modification

Several doses and dosing schedules of vorinostat have been utilized in the treatment of solid tumors and hematologic malignancies. The FDA approved dose is 400mg once a day for the treatment of cutaneous T-cell lymphoma. The MTD of vorinostat is 400mg daily or 200mg twice a day (BID) for continuous dosing without a resting period, or 300mg BID for 3 consecutive days per week for intermittent dosing. In phase I and II studies of vorinostat for the treatment of lymphomas, a range of doses and schedules have been used, including 400mg daily, 600mg daily, or 400mg BID continuously;[16] 200mg BID for 14 days followed by a 7-day break in 21-day cycles;[17, 19] 300mg BID followed by a 7-day break, which was subsequently modified to 300mg BID for 3 days followed by 4 days of rest;[58] and 100mg in

the morning/200mg in the evening for days 1-5 and 8-12 of a 21-day cycle.[87, 88] Anti-lymphoma activity was seen at all the above dose levels. While it is expected that vorinostat will have anti-lymphoma activity in this setting, as described above, the rationale for its use in this trial is its immunomodulatory effects. Therefore, we will employ an intermittent dosing schedule of days 1-5 and 8-12 of a 21-day cycle, which was well-tolerated in a phase I study of vorinostat combined with alisertib, an agent with overlapping toxicities with vorinostat.[87, 88] Because of the potential for overlapping toxicity and/or potentiation of the immune-related effects of pembrolizumab, we will pursue a dose-escalation, starting at a lower dose of vorinostat than the MTD - 100mg BID dosed per the above schedule.

4.6.4 Rationale for Additional Patients in Expansion Cohort

Monotherapy with PD-1 blockade does not produce durable remissions in the great majority of patients with R/R HL. Therefore, effective therapies for patients with R/R HL who have prior exposure to PD-1 blockade is a major unmet need. Among the initial 42 patients enrolled onto the study, there were 15 patients with prior exposure to PD-1 blockade and the results were extremely promising with 13 out of 15 patients achieving an objective response. Therefore, we will enroll an additional 10 patients with R/R HL who have prior anti-PD-1/PD-L1 exposure to more adequately explore the safety and anti-tumor activity of pembrolizumab plus vorinostat in this unique population. In addition, to minimize heterogeneity among PD-1/PD-L1 exposed patients (some could be PD1/PD-L1-exposed but still sensitive) we narrowed the eligibility to PD-1/PD-L1 refractory to focus on this particular group of patients where there is a high unmet need.

4.6.5 Rationale for Endpoints

4.6.5.1 Safety Endpoints

The primary endpoint is toxicity. Toxicity will be described by type, severity (according to NCI CTCAE v4.03), duration, reversibility, and attribution. Because of the unique immune-related adverse events (IrAEs) observed with checkpoint inhibitors, we will monitor for "unacceptable toxicity" with this new combination of drugs (defined in Section10.2). In this phase I study, safety, tolerability, and the determination of the MTD/RP2D are the primary endpoints. While pembrolizumab and vorinostat have been well-tolerated in clinical trials administered alone or in combination with other agents, we will assess the safety of this particular combination.

4.6.5.2 Efficacy Endpoints

In this phase I study, we aim to obtain a preliminary estimate of the anti-tumor activity of pembrolizumab plus vorinostat in patients with relapsed or refractory DLBCL, FL, or HL, as determined by the ORR. ORR is defined as the proportion of patients who achieve complete or partial response (CR+PR). Additional secondary endpoints for the study will be CR rate, time to response (TTR), duration of response (DOR), overall survival (OS) and progression-free survival (PFS). Each study agent, pembrolizumab and vorinostat, has demonstrated

activity in non-Hodgkin lymphoma (NHL) and HL. In FL and DLBCL, the ORR to either agent does not exceed 40-50%, and thus can be improved on. In early studies thus far, the ORR to PD-1 inhibition in HL appears to be high, ranging from 66-87%. However, the CR rate is low (< 20%) with either agent in DLBCL, FL, and HL. Therefore, an improvement in the ORR with combined vorinostat plus pembrolizumab therapy would be an exciting development in the field, particularly in DLBCL and FL, and would merit further study of the combination. Likewise, an improvement in CR rate would be a critically important development in optimizing PD-1 inhibitor therapy.

4.6.6 Rationale for Biomarker Research/Correlative Studies

Immunologic and genomic biomarkers have been associated with tumor response to immunotherapy, including checkpoint inhibitors like pembrolizumab. We propose to evaluate a series of exploratory immunologic and genomic correlatives to explore the association between each biomarker and response or resistance to combined pembrolizumab and vorinostat therapy. The correlative studies described below are exploratory in nature, and meant to be hypothesis-generating -they will not be powered for statistical significance. The below description is an anticipated rather than an exact list of studies that will be performed, as the investigators reserve the right to adjust the studies to be performed as techniques evolve and new data may become available that is relevant to the study agent and/or study population.

· Immunologic Biomarkers:

PD-L1 expression in tumor cells is a biomarker for response to anti-PD1 therapy in solid tumors.[89] PD-L1 expression has also been demonstrated in all HL patients tested who responded to PD-1 inhibition with pembrolizumab or nivolumab.[13, 14] Furthermore, the pattern and spatial relationship between PD-1 and PD-L1-expressing cells are associated with response in patients with melanoma treated with pembrolizumab.[27]

The presence, abundance, and composition of tumor infiltrating lymphocyte (TIL) populations in various tumor types are associated with clinical outcome.[90-92] In addition, the presence of certain TIL populations, particularly CD8+ T-cells, and their spatial orientation in tumors is associated with outcome after immunotherapy, including PD-1 blockade with pembrolizumab.[27, 93] Using high-resolution spectral analysis and automated scanning of tissue sections, the Lee laboratory at City of Hope has developed a technique for quantitative, spatial IHC analysis of TIL and other immune cell subsets in a tumor. The Lee lab has demonstrated that spatial grouping patterns of TILs and dendritic cells differ between tumor-draining lymph nodes and normal lymph nodes and are associated with outcome in patients with breast cancer.[94, 95]

We will evaluate the relationship between response to study therapy and PD-L1 expression and potentially other checkpoint receptors/ligands by immunohistochemistry (IHC) in pre-treatment tumor samples. We will perform quantitative, spatial immunofluorescence analysis using the Vectra system in the Lee laboratory, including PD-L1 and potentially other checkpoint receptors/ligands, dendritic cells, tumor associated macrophages,[96] TILs including

CD8+ cells and regulatory T-cells, and possibly other immune cell subsets and explore the association with response to study therapy. We will also analyze changes in immune cell subsets by flow cytometry on peripheral blood mononuclear cells (PBMCs) at baseline and during treatment and explore the association with response to study therapy. Cytokine analyses may be performed on the plasma portion of these samples.

· Genomic Biomarkers:

Genomic signatures define distinct subsets of DLBCL and are associated with outcome after standard therapy in patients with DLBCL, FL, HL.[97-101] Genomic studies have elucidated tumor target-specific and microenvironmental characteristics that predict response to novel immunotherapies, including checkpoint inhibitors. One key target-specific genomic biomarker of response to immunotherapy is a tumor's mutational burden. In clinical trials of melanoma patients treated with the anti-CTLA-4 antibody, ipilimumab, and non-small cell lung cancer (NSCLC) patients treated with pembrolizumab, patients with a higher mutational load in pre-treatment tumor samples have a higher rate of durable clinical benefit, objective response rate, and improved survival compared to patients with fewer mutations.[102, 103] Nonsynonymous genetic mutations result in the formation of neoantigens that improve recognition of the tumor by the host immune system, which appears to drive anti-tumor responses in the enhanced effector cell milieu created by checkpoint blockade. Similarly, in melanoma patients who have durable, complete responses after adoptive TIL therapy, specific neoantigens resulting from nonsynonymous mutations can be identified that are responsible for the robust anti-tumor responses observed.[104, 105]

In addition to a tumor's mutational profile, tumor gene expression patterns impact response to novel immunotherapies. Increased expression of genes that encode for immune-related targets, such as T-cell surface markers, immune receptors, and cytokines/chemokines, in pre-treatment melanoma tumor samples are associated with response to ipilimumab.[106] Similarly, overexpression of immune-related genes in pretreatment tumors of patients with melanoma and NSCLC is associated with outcome after treatment with an antigen-specific tumor vaccine and immunostimulant.[107]

We will explore whether total mutational burden or genomic signatures as determined, for example, by mutational or gene expression profiles in pre- (and post-treatment, if available) tumor samples are associated with response and outcome after vorinostat plus pembrolizumab therapy.

· Circulating DNA as biomarker:

The detection of circulating tumor DNA (ctDNA) has been studied in lymphoma. Next-generation sequencing (NGS)-based ctDNA detection performed by NGS of the immunoglobulin (Ig) or T-cell receptor genes can identify ctDNA in the peripheral blood mononuclear cells (PBMC) and plasma (cell-free DNA) at diagnosis in a range of lymphomas, including classical Hodgkin lymphoma and diffuse large B-cell lymphoma (DLBCL).[108-111] In addition, ctDNA levels correlate with treatment response in DLBCL, and the persistence or

recurrence of ctDNA during and after upfront therapy is associated with subsequent DLBCL relapse.[110, 111] In a small study using Ig-NGS in patients with FL, 85% of patients had a tumor clone identified from the diagnostic biopsy, and 83% had ctDNA in the peripheral blood at diagnosis. In patients who underwent observation without treatment and also patients treated with chemoimmunotherapy, higher ctDNA levels at diagnosis were associated with shorter progression-free survival (PFS).[112] While the Ig-NGS method is powerful, the investigation of only Ig genes limits its sensitivity, resulting in a sizable minority of patients in whom the assay is not applicable (ctDNA only detected in 73% of FL starting cohort). Meanwhile, ctDNA assessment using capture-based NGS for recurrent mutations and rearrangements has been explored in DLBCL, and the method appears feasible and highly sensitive.[113, 114] Like IgNGS, capture-based NGS MRD detection exploits the genetic features of a lymphoma to identify tumor-specific DNA in the peripheral blood of patients with lymphoma. Utilizing bioinformatics pipelines optimized for low input DNA, hybridization capture-based NGS is performed on a patient sample (i.e. peripheral blood, tumor tissue) that evaluates a panel of single-nucleotide variants (SNVs), insertions/deletions (indels), and chromosomal translocations known to be recurrently mutated in a specific lymphoma subtype (to date, primarily DLBCL). CtDNA can be quantitated by calculating the proportion of tumor-specific cfDNA molecules within a sample (the variant allele fraction). Thus far, studies have demonstrated that genetic alterations detected in ctDNA using capture-based NGS analysis of the peripheral blood are highly concordant with genetic alterations determined by NGS of a primary DLBCL tumor sample.[115-117] Similar to IgNGS, capture-based NGS based MRD detection can identify ctDNA in patients with DLBCL prior to treatment, can quantify ctDNA levels that track with treatment response and resistance, and can detect relapse prior to and at the time of clinically apparent relapse.[114-116, 118]

NGS-based ctDNA assessment methods have demonstrated initial promise in detecting ctDNA in HL. In early studies, IgNGS could identify a tumor clone for tracking using tumor tissue in 56-71% of HL patients and ctDNA was detected in the PBMC and/or plasma of 73% of those patients.[109, 119] In one study of ctDNA assessment in patients with lymphoma who had undergone allogeneic stem cell transplantation, out of two HL patients who relapsed, ctDNA was detected prior to and at the time of relapse in one patient and at the time of relapse in the other patient.[119] Using a separate NGS method, Vandenberghe et al. identified tumor-specific genomic imbalances in cfDNA from the plasma of HL patients with early or advanced stage disease at diagnosis that became undetectable after treatment response.[120] Finally, *XPO1* mutations could be detected at diagnosis in the plasma of patients with cHL and tracked after treatment using a digital PCR technology. The persistence of this mutation showed a possible association with relapse in patients a negative PET scan at end of treatment.[121]

We will explore the value of circulating DNA (ctDNA) as a biomarker of response to study therapy by next-generation sequencing (NGS) using blood samples collected during treatment.

· Quantitative PET assessment in HL and DLBCL:

- *In Hodgkin Lymphoma*

For better characterization of therapeutic response and prediction of outcome in patients with lymphoma, significant progress has been made in standardizing qualitative methods and integration of FDG PET in the international working group criteria (IWG) for lymphoma assessment.[122] However, there is a growing need for the development of quantitative imaging metrics as operator-independent surrogate measures to predict treatment response and survival. In this regard, standardized uptake values (SUV) have been the most widely used quantitative measure for assessing tumor metabolic activity and treatment response. In Hodgkin lymphoma (HL), SUVmax cut-off was investigated as a predictor of progression after two cycles of chemotherapy,[123] however, without validation studies to define a widely accepted cut off value, these criteria have not yet been adopted for HL.

The PET-derived whole body metabolic metrics, metabolically active tumor volume (MTV*) and total lesion glycolysis (TLG**) measure metabolic activity in an entire tumor mass to reflect tumor biology. With the recent development of software based automated assessments, volume-based metabolic parameters have become increasingly available quantitative PET (qPET) indices. Although these metrics have the potential to become a useful index for assessing treatment response and survival they are yet to be standardized and validated to translate to a clinical practice platform. Recent studies have reported that a high total MTV predicted a lower survival in various retrospective studies in HL showing variation in the strength of outcome prediction but promising data in early stage HL.[124-128] Based on these encouraging results, there is interest in utilizing qPET parameters, including MTV, to tailor treatment in HL, but these metrics require validated in larger, prospective studies. In addition, there is controversy with respect to the methodologies used among various investigators,[124, 125, 129] though studies that have evaluated different methodologies have shown similar utility to the various methods.[130] Preliminary results suggest that qPET metrics may not be applicable across treatment regimens. As part of the HD18 trial by the German Hodgkin Lymphoma Study Group Mettler et al found that baseline MTV was a predictive factor for early response to BEACOPP after two cycles. However, no prognostic value for end of treatment response and ultimate outcome was observed with an interim PET-adapted treatment strategy.[129] However, in the LYSA AHL2011 trial, which utilized a similar PET-adapted BEACOPP-based approach in advanced stage HL, MTV was prognostic for PFS. When combined with interim PET status, MTV and interim PET results together identified a subset of patients at high risk for treatment failure.[131]

In patients with relapsed or refractory HL treated with sequential BV followed by ICE chemotherapy (in patients not in complete response after BV), baseline MTV and TLG were found to be strong prognostic factors for outcome. In multivariate analyses, baseline MTV remained the main independently prognostic factor associated with treatment outcome along with end of treatment PET status, and baseline MTV enhanced the prognostic value of end of treatment PET status for outcome.[132] Thus, there are data to support the use of qPET parameters as a prognostic factor in HL, both alone and in combination with the dynamic response data gained with interim or end of treatment PET.

*MTV refers to the total volume, measured in cm^3 or ml, of the metabolically active tumor volume encompassed by a volume of interest (VOI), either for a single lesion or for multiple lesions.

**TLG is the product of SUV_{mean} in the defined VOI and the MTV; the rationale is to combine tumor burden and its metabolic activity, having an index that is correlated to both the volume and the uptake of the volume.

- *In DLBCL*

Several working groups have recognized quantitative measures as an important tool in staging and response assessment in DLBCL, for instance SUVmax or ΔSUVmax. Studies investigating the role of ΔSUVmax demonstrated its usefulness for response stratification in DLBCL.[133] Additionally, FDG-PET provides biomarkers such as the metabolic tumor volume (MTV) or total lesion glycolysis (TLG), which incorporate information concerning tumor burden and disease activity. Metabolic measures were reported to have a prognostic value in non-Hodgkin lymphoma. Mikhaeel et al. demonstrated that MTV at staging is an important prognostic factor for DLBCL and that combining MTV with results of early PET response assessment improves the predictive power.[134] Similar findings emerged from a recently published analysis including 510 DLBCL patients treated within the PET-guided therapy optimization trial PETAL.[135] Interestingly, it has been also shown that MTV is a valid prognosticator in elderly individuals with DLBCL receiving R-CHOP. A study by Vercellino and colleagues found high pretreatment MTV to be significantly associated with inferior PFS and OS in this group.[136] Including patients from the LNH073B study, a French working group additionally examined the role of radiomic features characterizing lesion dissemination and reported that combining them with baseline MTV further improves risk stratification in DLBCL patients.[137] Furthermore, several retrospective studies have shown in DLBCL that high baseline TMTV measured by fluorodeoxyglucose PET/CT was associated with worse progression-free survival (PFS) and/or OS.

The intention of this work is to validate the prognostic value of qPET metrics, in particular MTV, in a prospective trial incorporating novel immunotherapy into the treatment of relapsed/refractory HL and DLBCL.

Methods for Quantitative PET Assessment Studies

PET/CT scans are performed after 6–8 hours of fasting and after the intravenous administration of ~10–15 mCi (370–555 Mbq) of ^{18}F-FDG. After 50–70 minutes of radiotracer uptake, PET images are acquired on a non-contrast 16-slice PET/CT system (GE Medical Systems). Three-dimensional (3D) iterative reconstruction using a 168 × 168 matrix with a zoom of 1.0, FWHM filter of either 5.0 or 6.0 mm, and 2 iterations with 8 subsets is used generate PET images. The non-contrast whole body CT data is utilized for lesion anatomic localization and attenuation correction. ^{18}F-FDG PET/CT images region-of-interest (ROI) will be performed using the commercially available, FDA-approved "Mirada Medical PET/CT XD Oncology Review"

software (Mirada Medical) and SECTRA™. The ROI measurement - Standard uptake value (SUV; g/mL) – attempts to measure the normalized amount of radioactive concentration found on qualitative (visual) PET inspection in selected part of the body at a certain time. Some variation of the normalization factor for the SUV exist, including: body weight (SUVbw), lean body weight (SUVlbw), and body surface area (SUVbsa). Calculations reported in this study will rely on the general standard of care: SUVbw and it is calculated using the formula recommended by the QIBA SUV Subcommittee:

- SUVbw(pixel) in g/mL= activity (pixel) in (Bql/ml)/injected dose in Bql/patient weight in grams).

Image DICOM tags are used to perform the calculation, including: patient's weight, acquisition date time, radionuclide half-life and radiopharmaceutical start date/time.

The background red marrow of each patient is defined by using a 1 cm^3 diameter region of interest in the most inferior vertebral body which does not demonstrate focally increased FDG uptake or vertebroplasty material. Focal lesions for each patient are defined as focal areas, measuring at least 1 cm in diameter, not otherwise demonstrated to be artifacts by comparison with coregistered CT, recognizable as discrete foci of increased ^{18}F-FDG uptake on maximum intensity projection images (MIP), and exhibiting a max SUV (SUV_{max}) greater than the SUV_{max} for the patient's background red marrow.

The volume of each lesion and its 3D margins are determined by incorporating all contiguous pixels with activity greater than 0.1 g/mL above that of the background marrow. Because of the considerable statistical variability inherent in the acquisition, reconstruction, and display of accumulations of radiopharmaceuticals in the clinical imaging setting, SUVs obtained from larger regions of interest (ROI) are more reproducible than single pixel determinations such as SUV_{max}. For this reason, we have chosen to quantify activity by calculating the SUV_{max} defined as the average SUVs, corrected for lean body mass, of the pixels in a sphere 1.2 cm in diameter (1 cc) centered to include the most intense pixel.

The total MTV for disease in each patient is defined as the sum of MTVs of all the individual focal lesions identified in the analysis. The TLG of each focal lesion is calculated by multiplying the MTV of that lesion with its corresponding mean SUV (TLG = $SUV_{mean} \times$ MTV). The global TLG of each patient is defined as the sum of the TLGs for all the focal lesions in the analysis.

All volumes of interest that are drawn by the automated computer system will be evaluated by the reader to delete those regions that are not deemed to be associated with tumor. The review computer system will automatically calculate all quantitative assessments (SUVmax, MTV, TLG) for each lesion at baseline, mid therapy (when available) and end of therapy (EOT). In addition, at EOT, we will calculate the percentage of change from baseline for each qPET parameter.

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

Eligible patients must:

- Have a histologically confirmed diagnosis of follicular lymphoma, diffuse large B-cell lymphoma, or classical Hodgkin lymphoma according to the WHO classification, with hematopathology review at the participating institution.
    - FL: grade 1, 2, 3A, or 3B are eligible.
    - DLBCL: transformed indolent lymphomas (TIL), primary mediastinal large B-cell lymphoma (PMBCL), and aggressive B-cell lymphoma unclassified (BCL-U) are eligible.
    - HL: all classical HL subtypes are eligible except for nodular lymphocyte predominant Hodgkin lymphoma, which is excluded.

NOTE: Per Amendment (Protocol V9 dated 06-04-20), this study will only enroll HL patients who have had prior exposure to PD-1/PD-L1 immunotherapy. FL, DLBCL, and HL patients without prior exposure to PD-1/PD-L1 immunotherapy are no longer eligible.

- Patients with HL or DLBCL must refuse or not be candidates for curative autologous stem cell transplantation.
- Have relapsed or refractory disease after at least 1 prior regimen, including:
    - Recurrence of disease after a documented complete response (CR)
    - Progression of disease after a partial response (PR) to the prior regimen
    - Partial response (PR), stable disease (SD) or progressive disease (PD) at the completion of the prior treatment regimen. If a patient has PR to prior regimen without PD, there must be biopsy-proven residual disease that is measurable.

NOTE: Per Amendment (Protocol V10 dated 10-16-20), this study will only enroll HL patients who are *refractory* to PD-1/PD-L1 immunotherapy.
Refractory to PD-1/PD-L1 immunotherapy is defined as patients who had prior exposure to PD-1/PD-L1 immunotherapy and either - achieved a best response of SD or PD or - achieved a best response of CR/PR but developed PD while on active PD-1/PD-L1 treatment.

5.1.2 Subject Inclusion Criteria

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

1. Documented informed consent of the participant or legally authorized representative.
2. Be ≥ 18 years of age on day of signing informed consent.
3. Have measurable disease by CT or PET scan, with one or more sites of disease ≥ 1.5cm in longest dimension.
4. Be willing to provide tissue from a fresh core or excisional biopsy of a tumor lesion prior to starting study therapy or from archival tissue of a biopsy that was performed after the most recent systemic therapy.
5. Have a performance status of 0 or 1 on the ECOG Performance Scale.
6. Demonstrate adequate organ function as defined in Table 1, all screening labs should be performed within 14 days of treatment initiation.

Table 1. Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1,000 /mcL **Exception:** Unless documented bone marrow involvement by lymphoma.
Platelets	≥75,000 / mcL **Exception:** Unless documented bone marrow involvement by lymphoma.
Hemoglobin	≥8 g/dL without transfusion or EPO dependency (within 7 days of assessment) **Exception:** Unless documented bone marrow involvement by lymphoma.
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 ≤ 3X ULN if patient has Gilbert's disease **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 involvement by lymphoma as the etiology of transaminase elevation
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
[a]Creatinine clearance should be calculated by the Cockcroft-Gault equation	

7. Female subject 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.

8. Female subjects of childbearing potential (Section 7.11.2) must be willing to use an adequate method of contraception as outlined in Section 7.11.2 – Contraception, for the course of the study through 120 days after the last dose of study medication.

Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject.

9. Male subjects of childbearing potential (Section 7.11.2) must agree to use an adequate method of contraception as outlined in Section 7.11.2- Contraception, starting with the first dose of study therapy through 120 days after the last dose of study therapy.

Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject.

5.1.3 Subject Exclusion Criteria

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

1. Is currently participating and receiving study therapy or has participated in a study of an investigational agent and received study therapy or used an investigational device within 3 weeks of the first dose of treatment.

2. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment.

3. Has received a prior allogeneic hematopoietic stem cell transplant within the past 5 years, requires immunosuppression, or has evidence of active graft-versus-host-disease.

4. Has received prior autologous hematopoietic stem cell transplant within the last 60 days.

5. Has a known history of active TB (Bacillus Tuberculosis)

6. Severe hypersensitivity to pembrolizumab or any of its excipients.

7. Has had a prior anti-cancer monoclonal antibody (mAb) within 3 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 3 weeks earlier. If a patient has progressive or stable disease to prior regimen, rituximab is allowed up to 2 weeks prior to the initiation of study therapy.

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

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

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

9. Has taken valproic acid, or another histone deacetylase inhibitor, within 2 weeks prior to study Day 1.

10. 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.

11. Has known active central nervous system (CNS) involvement by lymphoma, including leptomeningeal involvement. Subjects with prior CNS involvement by lymphoma must have remission of the CNS component of the lymphoma. These subjects must have a baseline MRI during screening without evidence of new or enlarging brain lesions and must not have any new or progressive neurologic symptoms.

12. Has active autoimmune disease that has required systemic treatment in the past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (eg., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment. A history of hemolytic anemia associated with the lymphoma does not exclude a patient from the study.

13. Has a history of (non-infectious) pneumonitis that required steroids or current pneumonitis

14. Has an active infection requiring systemic therapy.

15. Has a QT interval corrected for heart rate (QTc) > 470 ms using the Fridericia formula. If the screening electrocardiogram (ECG) has a QTc > 470ms, the mean QTc of 3 ECGs can be utilized, but must be < 470 ms.

16. Is unable to swallow capsules, has a partial or small bowel obstruction, or has a gastrointestinal condition resulting in a malabsorptive syndrome (e.g. small bowel resection with malabsorption).

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

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

19. 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.

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

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

22. 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.

5.2 Inclusion of Women and Minorities

The study is open to anyone regardless of gender or ethnicity. Efforts will be made to extend the accrual to a representative population, but in a trial which will accrue approximately 52 subjects, a balance must be struck between subject safety considerations and limitations on the number of individuals exposed to potentially toxic or ineffective treatments on the one hand and the need to explore gender, racial, and ethnic aspects of clinical research on the other. If differences in outcome that correlate to gender, racial, or ethnic identity are noted, accrual may be expanded or additional studies may be performed to investigate those differences more fully.

6.0 PARTICIPANT ENROLLMENT

6.1 Pre-Enrollment Informed Consent and Screening Procedures

Diagnostic or laboratory studies performed exclusively to determine eligibility will be done only after obtaining written informed consent. As long as they were performed within the appropriate time frame, studies or procedures that are performed for clinical indications (not exclusively to determine study eligibility) may be used for baseline values and/or to determine pre-eligibility, even if the studies were done before informed consent was obtained. Reference is made to Section 8.0 - Study Calendar. The informed consent process is to be fully documented, and the prospective participant must receive a copy of the signed informed consent document.

6.2 Participant Enrollment

6.2.1 COH DCC Availability and Contact Information

Eligible participants will be registered on the study centrally by the DCC at City of Hope. DCC staff are available **between the hours of 8:00 a.m. and 5:00 p.m. PST, Monday through Friday (except holidays).** DCC contact information is as follows:

- e-mail: DCC@coh.org

6.2.2 Slot verification and reservation

During the dose escalation stage, eligible Phase 1 participants will be assigned a dose level (Section 7.0). Once the recommended phase 2 dose (RP2D) is defined, participants will enroll at the RP2D dose (expansion cohort).

Issues that would cause treatment delays should be discussed with the Principal Investigator.

Designated study staff should call the DCC to verify current slot availability, and to reserve a slot for a specific prospective subject.

The DCC should be notified of cancellations of prospective participants holding slots as soon as possible.

6.3 Screen Failures and Registered Participants Who Do Not begin Study Treatment

The DCC is to be notified of all participants who sign consent but do not meet eligibility criteria or do not initiate protocol therapy.

6.4 Registration Process

To register a participant, the subsequent procedure is to be followed.

1. The participating site's data manager/coordinator/research nurse should contact the DCC via telephone or email to provide notification regarding the pending registration and communicate desired timeline of the registration, especially if it must be completed promptly to meet the registration window.

2. The data manager/coordinator/research nurse should then e-mail copies to DCC@coh.org of the following documents to the DCC:
   - Completed Eligibility Criteria List (printed from Section 5.1 of the protocol)
   - Source documentation to support eligibility criteria**
   - Signed informed consent document
   - Signed HIPAA authorization form (if separate from the informed consent document)
   - Signed subject's Bill of Rights
3. After having received all transferred documentation, the DCC will complete the review the documents to verify eligibility, working with the study team as needed to resolve any missing required source elements. A participant failing to meet all protocol eligibility requirements will not be registered.
4. Once eligibility has been confirmed, DCC staff will send a Confirmation of Registration Form and signed eligibility checklist, including the participant study number to:
   - the COH Study PI and COH study team designees (including but not limited to study monitor(s) and statistician(s)).
5. Upon receipt of the Confirmation of Registration Form, COH study team will register the patient in OnCore.

7.0 TREATMENT PROGRAM

The agents to be used in this trial are outlined below in Table 2:

Table 2. Study Agents

Study Agents					
Drug	**Dose/Potency**	**Dose Frequency**	**Route of Administration**	**Regimen/Treatment Period**	**Use**
Pembrolizumab	200 mg	Q3W	IV infusion	Day 1 of each 21-day cycle	Experimental
Vorinostat	100mg capsules, dose will vary by dose level	BID	Oral	Per Dose Escalation rules	Experimental

7.1 Treatment Allocation

There will be no randomization or stratification as part of this study. All patients who consent to the study, meet eligibility criteria, and are registered on the trial will receive study treatment.

This is a phase I study, including a dose-escalation portion of the study with 2 dose levels and 2 possible de-escalation dose levels, for a total of 4 possible dose levels. The starting dose will

be 100mg of vorinostat twice a day (BID), and 200mg IV pembrolizumab. Subjects will receive oral vorinostat according to dose level schedule and dose. Pembrolizumab will be administered on day 1 of each cycle thereafter. Study therapy will be administered in 21-day cycles. The planned dose levels in the dose-escalation portion of the study are outlined in Table 3 below.

Once the RP2D has been determined, an expansion cohort of 40 patients will be enrolled and treated at the RP2D, to acquire additional safety and tolerability data about the combination.

Table 3. Phase I Dose Levels

Dose Level	Vorinostat	Pembrolizumab (day 1)
-2	100mg PO BID, d1-3, 8-10	200mg IV
-1	100mg PO BID, d1-3, 8-10, 15-17	200mg IV
1 (starting)	100mg PO BID, d1-5, 8-12	200mg IV
2	200mg PO BID, d1-5, 8-12	200mg IV

7.1.1 Treatment Duration

Study treatment will continue until the subject completes 24 months of treatment with the study regimen, or experiences radiographically-confirmed PD (Section 9.2.6 and Section 9.2.6.1), unacceptable adverse experiences, either DLT (Section 7.2) or other unacceptable toxicity (section 10.2), or meets other criteria for study withdrawal or treatment discontinuation

7.1.2 Rules for Phase I Dose Escalation, De-Escalation and Expansion: Adapted Rolling 6 Design

This phase I trial will employ a modified Rolling 6 design, a more conservative version of the Rolling 6 design of Skolnik, et al [29]. In this design, at most, 3 patients will be under observation for DLT on the current test dose level at any time. Patients who are not evaluable for DLT will be replaced. Once each patient is evaluable for toxicity and passes without a DLT, an additional patient *may* be accrued on that dose level – up to 6 patients. Once 3 patients are evaluable with no patient at that dose level experiencing a DLT, the dose can be escalated, or up to 3 additional patients may be treated at the current dose level. Although this design does not require that 6 patients be treated, no more than 6 evaluable patients will be accrued to any dose level during the dose finding portion of this study. If at any time, the dose level has 1 documented DLT with fewer than 6 evaluable patients, accrual will continue until 6 patients are evaluable. Escalation will terminate as soon as two or more patients experience any DLT attributable to the study treatment, at a given dose level. MTD will be declared at the highest dose level at which 6 patients have been treated and at most 1/6 patients experiences DLT. If more than 1/6 patients experiences DLT, then the next lower dose will be expanded. There will be no intrapatient dose escalation. These rules are outlined in Table 4:

Table 4. Dose Escalation Rules

# Patients on Current Level			Action
With DLT^	Evaluable	Evaluable + At Risk^	
0	0	1-2	Accrue next patient at this level*
0	0	3	Hold accrual
0	1	1-3	Accrue next patient at this level
0	1	4	Hold accrual
0	2	2-4	Accrue next patient at this level
0	2	5	Hold accrual
0	3-6	3-6	Accrue next patient at the next higher level*,+
1	1	1-2	Accrue next patient at this level
1	1	3	Hold Accrual
1	2	2	Accrue next patient at this level
1	2	3-4	Hold accrual
1	3-5	3-5	Accrue next patient at this level
1	3-5	6	Hold accrual
1	6	6	Accrue next patient at the next higher level*
2**	any	any	Accrue next patient at next lower level (max 6)

^: DLT: a patient with a documented DLT
Evaluable: a patient who is either fully evaluable for toxicity for the purpose of dose escalations or has a DLT
At Risk: a patient who is on treatment and has not yet passed the evaluation period nor had a DLT

*: During the dose-escalation portion, if higher dose level is already closed, the next lower dose will accrue to a total of 6 patients, with 2 or higher DLTs requiring further dose de-escalation.

+: Although under this scenario escalating to the next higher dose level is suggested, additional patients can be accrued to the current level -up to n=6 patients.

**: Patients treated on a higher dose will have their treatment modified to the dose below the dose level with 2 DLTs, if pending patients have DLT.

7.2 Definition of Dose-Limiting Toxicity

The dose-limiting toxicity (DLT) observation period will be 42 days (2 cycles). DLT assessment will occur on cycle 3, day 1 prior to receipt of cycle 3, day 1 of study therapy. Toxicities will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE, Version 4.03) accessible at:

http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

DLT will be defined as one of the following AEs that is at least possibly related to study treatment.

Hematologic

- Grade 4 neutropenia lasting > 7 days (despite the use of growth factor support).
- Grade 4 thrombocytopenia lasting > 7 days or requiring platelet transfusion.
- Grade 3 or 4 thrombocytopenia associated with grade 2 or higher bleeding.
- Grade 4 anemia not associated with lymphoma.

- Any Grade 5 AE.

Non-hematologic

- Grade ≥ 3 pneumonitis that does not resolve to grade ≤ 1 within 3 days after initiation of supportive care measures.
- Any clinically relevant grade 3 or grade 4 AE with the exception of:
  - Grade 3 asymptomatic laboratory abnormalities, including lipase or amylase, that are not clinically relevant, not requiring hospitalization or delay of treatment.
  - Grade 4 laboratory abnormalities including, but not limited to, hypo- or hyperglycemia, hypo- or hypernatremia, hypo- or hyperkalemia, hypo- or hypermagnesemia, hypo- or hyperphosphatemia, or hyperuricemia that resolve within 48 hours to Grade ≤ 2 with supportive measures.
  - Grade 3 nausea, or fatigue controlled with supportive measures.
  - Grade 3 vomiting if the subject does not require total parenteral nutrition (TPN), tube feeding, or hospitalization, and the toxicity improves to < grade 3 within 72 hours.
  - Grade 3 asymptomatic endocrinopathy.
  - Grade 3 fatigue related to endocrinopathy that resolves within 7 days of hormone-replacement or corticosteroid therapy.
  - Grade 3 local inflammatory response attributed to local antitumor response.
  - Vitiligo or alopecia of any grade.
- Any Grade 5 AE.

7.3 Definition of the MTD and Recommended Phase II Dose

Dose escalation will proceed according to the schema outlined in Table 4. The maximum tolerated dose (MTD) is defined as the highest dose level at which < 33% of evaluable subjects experienced DLT, when at least 6 patients were treated at that dose level. The MTD will be considered the recommended phase II dose (RP2D), however the principal investigator may ultimately choose a lower dose level as the RP2D, depending on toxicity considerations, dose reduction on subsequent cycles, and other considerations.

7.4 Replacement of Subjects

During the Phase I dose escalation portion of the study, subjects will be replaced for any of the following:

- Missed 30% or more doses of vorinostat during the DLT period (not due to DLT).
- Did not receive the dose of pembrolizumab during the DLT period.
- Study drug discontinuation for any reason other than DLT during the DLT period.

Subjects who are replaced for missed doses may continue to receive study treatment if there is clear clinical benefit, but will not be included in DLT analysis.

During the expansion cohort portion of the study, subjects who discontinue study therapy prior to the first tumor response assessment for a reason other than progressive disease will be replaced.

7.5 Expansion Cohort

Once the RP2D has been determined, an expansion cohort of 40 patients will be enrolled and treated at the RP2D, to acquire additional safety and tolerability data about the combination. Toxicity monitoring will continue during the expansion segment. In addition, because of the unique immune-related adverse events (IrAEs) observed with checkpoint inhibitors, we will monitor for "unacceptable toxicity" with this new combination of drugs (defined in Section10.2). If >3 "unacceptable toxicity" events occur in the first 12 patients (≥33%) treated (across disease subtypes) at RP2D, or at a rate ≥33% thereafter at the quarterly review, we will halt accrual to fully evaluate these events and assess whether the regimen should be modified.

7.6 Study Treatment: Pembrolizumab

7.6.1 Dose Selection/Modification

7.6.1.1 Pembrolizumab 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 and Section 7.6.2.

7.6.1.2 Pembrolizumab Dose Modification (Escalation/Titration/Other)

Note: If pembrolizumab administration is held for toxicity, and the toxicity is most likely attributed to pembrolizumab and not attributed to vorinostat, administration of vorinostat can continue.

During the Phase I portion of the study, no intrapatient dose de-escalation will be allowed during the DLT period. After the DLT period, the following dose modifications are permitted for pembrolizumab-related adverse events according the guidelines outlined below in Table 5 for pembrolizumab. If, according to Table 5, pembrolizumab is discontinued permanently, the patient should continue to receive vorinostat.

Adverse events (both non-serious and serious) associated with pembrolizumab exposure may represent an immunologic etiology. These immune-related adverse events may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than on body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue pembrolizumab and administer corticosteroids. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab are provided in Table 5.See Section 7.10.1 for supportive care guidelines, including use of corticosteroids.

Table 5. Dose modification and toxicity management guidelines for immune-related AEs associated with pembrolizumab

General instructions:

1. Corticosteroid taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 4 weeks.
2. For situations where pembrolizumab has been withheld, pembrolizumab can be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered. Pembrolizumab should be permanently discontinued if AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks.
3. For severe and life-threatening irAEs, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids.

Immune-related AEs	Toxicity grade or conditions (CTCAEv4.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment • Add prophylactic antibiotics for opportunistic infections
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue		

Diarrhea / Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus). • Participants with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
	Grade 4	Permanently discontinue		
AST / ALT elevation or Increased bilirubin	Grade 2	Withhold	• Administer corticosteroids (initial dose of 0.5- 1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable
	Grade 3 or 4	Permanently discontinue	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold	• Initiate insulin replacement therapy for participants with T1DM • Administer anti-hyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes.
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated.	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hyperthyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hypothyroidism	Grade 2-4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyroinine) per standard of care	• Monitor for signs and symptoms of thyroid disorders.

Nephritis and Renal dysfunction	Grade 2	Withhold	• Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper.	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1 or 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
All other immune-related AEs	Intolerable/ persistent Grade 2	Withhold	• Based on type and severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3	Withhold or discontinue based on the type of event. Events that require discontinuation include and not limited to: Gullain-Barre Syndrome, encephalitis		
	Grade 4 or recurrent Grade 3	Permanently discontinue		

1. Withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician.

NOTE:

For participants with Grade 3 or 4 immune-related endocrinopathy where withhold of pembrolizumab is required, pembrolizumab may be resumed when AE resolves to ≤ Grade 2 and is controlled with hormonal replacement therapy or achieved metabolic control (in case of T1DM).

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 overall study PI. The reason for interruption should be documented in the patient's study record.

7.6.2 Pembrolizumab Administration and Storage

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 8.0). Trial treatment may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons.

All trial treatments will be administered on an outpatient basis.

Pembrolizumab is supplied free of charge by Merck and Co.

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.

Pembrolizumab Solution for Infusion is a sterile, non-pyrogenic aqueous solution supplied in single-use Type I glass vial containing 100 mg/4 mL of pembrolizumab. The product is preservative-free, latex free solution which is essentially free of extraneous particulates.

Pembrolizumab (MK-3475) Solution for Infusion vials are filled to a target of 4.25mL (106.25mg) to ensure recovery of 4.0mL (100mg).

Pembrolizumab (MK-3475) Solution for Infusion, 100 mg/ 4 mL vial: pembrolizumab Solution for Infusion vials should be stored at refrigerated conditions 2 - 8 °C (36 - 46 °F) and protected from light. Do not shake and do not freeze. Vials should be stored in the original box to ensure the drug product is protected from light.

Pembrolizumab (MK-3475) infusion solutions should be prepared in **0.9% Sodium Chloride Injection, USP** (normal saline) or regional equivalent or 5% Dextrose Injection, USP (5% dextrose) or regional equivalent and the final concentration of pembrolizumab in the infusion solutions should be between 1 mg/mL and 10 mg/ml.

The infusion solution should be administered through an intravenous line containing a sterile, non-pyrogenic, low-protein binding, 0.2 micron to 5 micron in-line or add-on filter.

Pembrolizumab should not be mixed with other diluents.
From a microbiological point of view, diluted solution should be used as soon as possible after preparation.

Pembrolizumab solutions (which contain no preservative) may be stored at room temperature for a cumulative time of up to 6 hours. The 6-hour countdown begins when the vial is pierced and includes room temperature storage of admixture solutions in the IV bags and the duration of infusion. (Please note this 6-hour timeframe is to provide a microbial control strategy. The microbial clock only starts when the product stopper is pierced and not when the vial is removed from the refrigerator.)
In addition, IV bags may be stored under refrigeration at 2°C to 8°C (36 °F to 46 °F), total cumulative storage time at room temperature and refrigeration should not exceed 24 hours.

Temperature monitoring records are required when pembrolizumab admixture solution is refrigerated during storage or transfer. Only a period with recorded 2-8 °C can be accounted

for refrigerated time. Time when temperature is above 8 °C and below 25°C should be deducted from a 6-hour room temperature storage time bucket.

If refrigerated, allow the IV bags to come to room temperature prior to use.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Discard the drug product vial if visible particles are observed. In addition, the following precautions should be observed:

- **Do not use pembrolizumab if discoloration is observed.**
- **Do not shake or freeze the vial(s).**
- **Do not administer the product as an intravenous (iv) push or bolus.**
- **Do not combine, dilute or administer it as an infusion with other medicinal products.**

7.7 Study Treatment: Vorinostat

Chemical Name: N-hydroxy-N'-phenyl-octane-1,8-diotic acid diamide; N-hydroxyl-N'-phenyl (9CI) octanediamide; suberoylanilide hydroxamic acid

Other Names: SAHA, L-001079038, WIN 64652, MSK390, AP390

Classification: Antineoplastic
CAS Registry Number: 149647-78-9

Molecular Formula: $C_{14}H_{20}N_2O_3$ **M.W.:** 264.32

Approximate Solubility: Water ≤ 5 mg/mL

Description: Histone deacetylase (HDAC) inhibitor

Mode of Action: Histone deacetylases (HDACs) are a family of enzymes that regulate chromatin remodeling and gene transcription via the dynamic process of acetylation and deacetylation of core histones.

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

How Supplied: Vorinostat is supplied free of charge by Merck and Co., Inc. Vorinostat is supplied as a white, opaque gelatin, size 3 capsule, containing 100 mg of vorinostat.

The inactive ingredients contained in each capsule are microcrystalline cellulose, sodium croscarmellose, and magnesium stearate.

Vorinostat 100 mg capsules are supplied in bottles containing 120 capsules.

Storage: Store vorinostat capsules at 20-25ºC. Excursions permitted between 15 and 30 ºC (59 to 86 ºF).

Stability: Shelf life stability studies of the intact bottles are on-going.

Route of Administration: Orally

Method of Administration: Unless otherwise stated in the protocol, vorinostat capsules must be administered whole. It is recommended that vorinostat be taken with food.

Patients should not make up missed doses. If a patient has an episode of emesis after taking vorinostat, patient should be instructed not to take an additional dose.

Potential Drug Interactions: The major pathways of vorinostat metabolism involve glucuronidation and β-oxidation. As vorinostat is not eliminated via CYP450 pathways, no drug-drug interactions are expected with known CYP450 inhibitors or inducers. Although vorinostat was not a potent reversible CYP450 inhibitor, studies performed to monitor gene expression changes indicated some potential for CYP2C9 and CYP3A4 activity suppression. However, these changes were observed at concentrations higher than the pharmacologically relevant concentration of 2 μM (Cmax).

Prothrombin time and INR prolongations have been reported in patients taking vorinostat concomitantly with coumarin derivative anticoagulants. Monitor these patients more frequently for alterations in their coagulation parameters.

Special Handling: Vorinostat is an anticancer drug. Clean powder spills from broken or damaged vorinostat capsules carefully minimizing inhalation. Wash spill area at least 3 times with ethyl alcohol, followed by water.

Patient Care Implications: Because vorinostat's dose limiting toxicities are anorexia, dehydration, diarrhea, and fatigue, patients should maintain adequate fluid and food intake. Encourage patients to seek a nutritional consult. Patients should be instructed to drink at least 2 liters of fluids daily to prevent dehydration.

Treat diarrhea promptly with appropriate supportive care, including loperamide. Instruct patients to begin taking loperamide at the first signs of: 1) poorly formed or loose stool, 2) occurrence of more bowel movements than usual in one day, or 3) unusually high volume of stool. Loperamide should be taken in the following manner: 4 mg at first onset of diarrhea, then 2 mg after each unformed stool. Daily dose should not exceed 16 mg/day. Loperamide should not be taken

prophylactically. Advise patients to drink plenty of clear fluids to help prevent dehydration caused by diarrhea. Avoid loperamide if there is the presence of blood or mucus in the stool or if diarrhea is accompanied by fever. If grade 3 or 4 diarrhea develops, discontinue further treatment with vorinostat.

Patients should not have taken valproic acid, another histone deacetylase inhibitor, for at least 2 weeks prior to study enrollment.

7.7.1 Vorinostat Dose/Delay Modification Guidelines

Note: If vorinostat is dose-reduced or held for toxicity, and the toxicity is most likely attributed to vorinostat and not attributed to pembrolizumab, administration of pembrolizumab can continue.

Vorinostat dose reductions are NOT permitted during the DLT period. Following the completion of the DLT period, the vorinostat doses may be modified for toxicity according to the below guidelines in Tables 6 and 7. Vorinostat dose delays are permitted during the DLT period due to study treatment-related toxicity, however, if a patient misses > 30% of the vorinostat doses due to toxicity, this will be considered a DLT.

Table 6. Vorinostat Dose Reduction Guidelines

Vorinostat Dose Reductions				
Starting dose	**1st dose reduction**	**2nd dose reduction**	**3rd dose reduction**	**4th dose reduction**
Dose Level 1	Dose Level -1	Dose Level -2	Dose Level -2 schedule but 100mg daily	N/A**
Dose Level 2	Dose Level 1	Dose Level -1	Dose Level -2	Dose Level -2 schedule but 100mg daily
mg = milligrams; po = orally; BID = twice daily				

**Patients requiring a dose reduction to below 100 mg daily of vorinostat at dose level -2 schedule will discontinue vorinostat permanently.

Table 7. Vorinostat Dose Delay Guidelines

Grade of Event	**Management/Next Dose for Vorinostat**
≤ Grade 1	No change in dose.

Grade 2	If tolerable to patient, no change needed but monitor patient more frequently. If intolerable to patient, hold* drug until toxicity ≤ Grade 1 then resume drug at same dose.
Grade 3 (1st occurrence)	Hold* until ≤ Grade 1. Resume at same dose.
Grade 3 (after 1st dose reduction)	Hold* until ≤ Grade 1: if toxicity related to drug, resume at 1 dose lower; if toxicity not related to drug, resume at same dose or 1 dose lower.**
Grade 3 (subsequent occurrences)	Hold* until ≤ Grade 1: if toxicity related to drug, resume at 1 dose lower; if toxicity not related to drug, resume at same dose or 1 dose lower**.
Grade 4	Discontinue vorinostat. However, if patient is clearly benefiting from treatment, may continue after recovery to ≤ Grade 1 at PI's discretion.
*If optimally managed, patients requiring a delay of >2 consecutive weeks will discontinue vorinostat **Patients requiring a dose reduction to below 100 mg daily of vorinostat at dose level -2 schedule will discontinue vorinostat permanently.	

7.8 Trial Blinding/Masking

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

7.9 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.

7.9.1 Acceptable Concomitant Medications

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

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

Use of growth factors, including filgrastim or pegfilgrastim and erythropoietin, is permitted per institutional policy and in accordance with American Society of Clinical Oncology (ASCO) guidelines.[138] Red blood cell transfusions are permitted per institutional guidelines. Platelet transfusions are permitted, but will be considered a DLT if required during the DLT period.

7.9.2 Prohibited Concomitant Medications

Subjects are prohibited from receiving the following therapies during the Screening and Treatment Phase 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 those specified in this protocol
- Radiation therapy
- 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. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.
- Other histone deacetylase inhibitors (e.g. valproic acid).

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 that are prohibited in this trial.

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

7.10 Rescue Medications & Supportive Care

7.10.1 Supportive Care Guidelines

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator. Use of growth factors, including filgrastim or pegfilgrastim and erythropoietin, is permitted per institutional policy and in accordance with American Society of Clinical Oncology (ASCO) guidelines.[138] Red blood cell transfusions are permitted per institutional guidelines. Platelet transfusions are permitted, but will be considered a DLT if required during the DLT period.

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

Note: if after the evaluation the event is determined not to be related, the investigator does not need to follow the treatment guidance (as outlined below). Refer to Section 7.6.1 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.

Please review the ECI document in detail for management of IrAEs and corticosteroid dosing, the below is meant to be a quick reference.

- **Myocarditis**
    - For suspected immune-mediated myocarditis, ensure adequate evaluation to exclude other etiologies.
    - Administer corticosteroids as appropriate.
- **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.

- **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. Supportive care with loperamide or other standard anti-diarrheal medication is acceptable. For Grade 2 or higher diarrhea, consider GI consultation and endoscopy to confirm or rule out colitis.
  - For **Grade 2 diarrhea/colitis,** administer oral corticosteroids.
  - For **Grade 3 or 4 diarrhea/colitis,** 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**: Pembrolizumab may cause severe or life threatening infusion-reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion.

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

Table 8. Pembrolizumab 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 participant is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g. from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the participant should be premedicated for the next scheduled dose. **Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment**	Participant may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of analgesic).
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: Epinephrine** IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Oxygen Pressors Corticosteroids Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. **Participant is permanently discontinued from further study drug treatment.**	No subsequent dosing
Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE) at http://ctep.cancer.gov		

7.11 Diet/Activity/Other Considerations

7.11.1 Diet

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

7.11.2 Contraception

Study treatment may have adverse effects on a fetus in utero. Furthermore, it is not known if study treatment has transient adverse effects on the composition of sperm.

For this trial, male subjects will be considered to be of non-reproductive potential if they have azoospermia (whether due to having had a vasectomy or due to an underlying medical condition).

Female subjects will be considered of non-reproductive potential if they are either:

(1) postmenopausal (defined as at least 12 months with no menses without an alternative medical cause; in women < 45 years of age a high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. In the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.);

OR

(2) have had a hysterectomy and/or bilateral oophorectomy, bilateral salpingectomy or bilateral tubal ligation/occlusion, at least 6 weeks prior to screening;

OR

(3) has a congenital or acquired condition that prevents childbearing.

Female and male subjects of reproductive potential must agree to avoid becoming pregnant or impregnating a partner, respectively, while receiving study drug and for 120 days after the last dose of study drug by complying with one of the following:

(1) practice abstinence[†] from heterosexual activity;

OR

(2) use (or have their partner use) acceptable contraception during heterosexual activity.

Acceptable methods of contraception are[‡]:

Single method (one of the following is acceptable):

- intrauterine device (IUD)
- vasectomy of a female subject's male partner
- contraceptive rod implanted into the skin

Combination method (requires use of two of the following):

- diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide)
- cervical cap with spermicide (nulliparous women only)
- contraceptive sponge (nulliparous women only)
- male condom or female condom (cannot be used together)
- hormonal contraceptive: oral contraceptive pill (estrogen/progestin pill or progestin-only pill), contraceptive skin patch, vaginal contraceptive ring, or subcutaneous contraceptive injection

†Abstinence (relative to heterosexual activity) can be used as the sole method of contraception if it is consistently employed as the subject's preferred and usual lifestyle and if considered acceptable by local regulatory agencies and ERCs/IRBs. Periodic abstinence (e.g., calendar, ovulation, sympto-thermal, post-ovulation methods, etc.) and withdrawal are not acceptable methods of contraception.

‡If a contraceptive method listed above is restricted by local regulations/guidelines, then it does not qualify as an acceptable method of contraception for subjects participating at sites in this country/region.

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 subjects of childbearing potential must adhere to the contraception requirement (described above) from the day of study medication initiation (or 14 days prior to the initiation of study medication for oral contraception) throughout the study period up to 120 days after the last dose of trial therapy. If there is any question that a subject of childbearing potential will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

7.11.3 Use in Pregnancy

If a subject inadvertently becomes pregnant while on study treatment, 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 14.2.2.

7.11.4 Use in Nursing Women

It is unknown whether study treatment (pembrolizumab or vorinostat) 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.

7.12 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 9.5.2 - 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: A subject may be granted an exception to continue on treatment with confirmed radiographic progression if clinically stable or clinically improved, please see Section 9.5.3.5

- Unacceptable adverse experiences, either DLT (Section 7.2) or other unacceptable toxicity (Section 10.2).
- Intercurrent illness that prevents further administration of treatment

- Investigator's decision to withdraw the subject
- The subject has a confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements
- The subject is lost to follow-up
- Completed 24 months of uninterrupted treatment with pembrolizumab or 35 administrations of study pembrolizumab, whichever is later.

  Note: 24 months of study medication is calculated from the date of first dose.
- Administrative reasons

The End of Treatment and Follow-up visit procedures are listed in Section 8 (Protocol Flow Chart) and Section 9.5.3 (Visit Requirements). After the end of treatment, each subject will be followed for 30 days for adverse event monitoring (serious adverse events will be collected for 90 days after the end of treatment). 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 for overall survival until death, withdrawal of consent, or the end of the study (last patient off therapy), whichever occurs first.

7.12.1 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 study treatment and had at least two cycles of study treatment beyond the date when the initial CR was declared.

7.13 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.

8.0 TRIAL FLOW CHART (STUDY CALENDAR)

8.1 Study Flow Chart

Trial Period:	**Screening Phase**	**Treatment Cycles[a]**													**End of Treatment**	**Post-Treatment**	
		1			**2**	**3**	**4**		**To be repeated beyond 8 cycles** **5**	**6**	**7**	**8**					
Treatment Cycle/Title:		D 1	D 8	D 15	D 1	D 1	D 1	D 15	D 1	D 1	D 1	D 1	D 15	Discon	Safety Follow-up	Follow Up Visits[g]	Survival Follow-Up
Scheduling Window (Days):	-28 to D1		± 3	± 3	± 3	± 3	± 3	See b	± 3	± 3	± 3	± 3	See b	At time of Discon[l]	30 days post discon[m]	Every 12 weeks post discon[†]	
Administrative Procedures																	
Informed Consent	X																
Inclusion/Exclusion Criteria	X																
Demographics and Medical History	X																
Prior and Concomitant Medication Review	X																
Post-study anticancer therapy status															X	X	X
Survival Status		X			X	X	X		X	X	X	X		X	X	X	X
Clinical Procedures/Assessments																	
Vorinostat administration		X			X	X	X		X	X	X	X					
Pembrolizumab administration		X			X	X	X		X	X	X	X					
Review Adverse Events		X	X		X	X	X		X	X	X	X		X	X		
Physical Examination	X	X	X		X	X	X		X	X	X	X		X	X		
Vital Signs, Weight, and oxygen saturation	X	X	X		X	X	X		X	X	X	X		X	X		
ECOG Performance Status	X	X	X		X	X	X		X	X	X	X		X	X		
Buccal swab		X															
Laboratory Procedures/Assessments: analysis performed by LOCAL laboratory																	

Trial Period:	**Screening Phase**	**Treatment Cycles[a]**												**End of Treatment**	**Post-Treatment**	
		1			**2**	**3**	**4**		**To be repeated beyond 8 cycles** **5**	**6**	**7**	**8**				
Treatment Cycle/Title:		D 1	D 8	D 15	D 1	D 1	D 1	D 15	D 1	D 1	D 1	D 1	D 15	Discon	Safety Follow-up	Follow Up Visits[g]	Survival Follow-Up
Scheduling Window (Days):	-28 to D1		± 3	± 3	± 3	± 3	± 3	See b	± 3	± 3	± 3	± 3	See b	At time of Discon[l]	30 days post discon[m]	Every 12 weeks post discon[†]	
Pregnancy Test - Urine or Serum β-HCG[n]	X**	X			X	X	X		X	X	X	X		X	X		
PT/INR and aPTT*	X																
CBC with Differential*	X	X	X	X	X	X	X		X	X	X	X		X	X		
Comprehensive Serum Chemistry Panel[c*]	X	X	X	X	X	X	X		X	X	X	X		X	X		
Urinalysis*	X																
T3, FT4 and TSH (thyroid panel)		X				X			X					X			
12-lead ECG	X	X			X	X	X		X					X			
Efficacy Measurements																	
PET-CT or CT N/C/A/P[e]	X							X					X	X[k]		X[d]	
Tumor Biopsies/Archival Tissue Collection/Correlative Studies Blood																	
Archival or Newly Obtained Tumor Tissue Collection	X													X[f]			
Bone Marrow Aspirate and Biopsy[j]	X[j]																
Correlative Studies Blood Collection		X			X				X[i]					X[h]			

* Should be performed within 14 days of treatment initiation. After Cycle 1, pre-dose laboratory procedures can be conducted up to 72 hours prior to dosing.

** 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.

† Imaging time point will be every 12 weeks (± 7 days) during the first year, and every 18 weeks thereafter (± 7 days).

a Vorinostat and pembrolizumab will be administered according to dose level in the Phase I dose-escalation portion of study and at RP2D in the expansion cohort portion of study. Vorinostat will be administered according to dose level, pembrolizumab will be administered on day 1 of each cycle. Cycle length will be 21 days.

b Should be performed between Day 15 and Day 21 (-3 days).

c Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH (only for DLBCL and FL patients), potassium, total protein, SGOT [AST], SGPT [ALT], sodium, uric acid, phosphorus, magnesium and direct bilirubin (if total bilirubin is elevated above the upper limit of normal).

d After 1 year, the imaging time point will occur every 18 weeks (+/- 7 days).

e PET-CT or CT N/C/A/P will be performed on cycle 4 day 15-21 (-3 days), cycle 8 day 15-21 (- 3 days), and every 4 cycles thereafter on day 15-21 (-3 days). Note: if there is no evidence of neck involvement by lymphoma at baseline, CT of chest, abdomen and pelvis (C/A/P) can be performed instead of N/C/A/P at subsequent re-staging. See sections 9.2.6 and 10.1 for additional imaging details.

f Collection of tumor tissue (fresh or archival) from standard of care tumor biopsy performed at the time of lymphoma relapse/progression, unless the tumor is inaccessible or there is a safety concern.

g Study follow-up period for subjects who remain on study but discontinue study treatment for a reason other than PD will remain on study and continue onto the Study Follow-up Period, and scans should be performed every 12 weeks (and then every 18 weeks after the first year, see †) starting from last on-treatment scan.

h For participants who progress during this study: Efforts should be made to collect a blood sample (if not collected within the last 30 days) at a planned SOC visit or a protocol visit. It will not be a deviation if the SOC visit/protocol visit falls outside of the ± 30 day window.

i For FL participants who end treatment for reasons other than progression: Collect at ~3 months (± 7 day) and ~6 months (± 7 day) at a planned SOC visit or a protocol visit. It will not be a deviation if the planned SOC visit/COH protocol visit falls outside of the ± 7 day window.

j A screening bone marrow biopsy is not required for HL patients, but can be performed for staging purposes at investigator discretion. For FL and DLBCL patients: - if a bone marrow biopsy was performed within 3 months prior to Day 1 and was negative, patients do not need to have a bone marrow biopsy performed at screening (unless clinically indicated), - if a bone marrow biopsy was previously performed and was positive, then the patient will have a bone marrow biopsy at screening, unless this previous bone marrow biopsy was performed within 3 months prior to Day 1 and patient did not have any systemic therapy in the meantime. Following initial screening, unless clinically indicated, bone marrow specimens will be collected only to confirm CR, and only on patients who had bone marrow involvement at baseline.

k PET-CT (or CT) at time of discontinuation will only be performed in patients who discontinue treatment for progression. Note: if a previous scan was obtained within 4 weeks prior to the date of discontinuation, then repeating the scan at treatment discontinuation is not mandatory.

l Assessments to be performed within 10 days of treatment discontinuation (except tumor imaging, see footnote k). Assessments performed after last dose of study agent and within 7 days of the decision to end treatment may serve as EOT assessments.

m Safety visit to occur 30 (-2/+7) days post-last dose of protocol therapy. Safety follow up may be extended until resolution/stabilization of reportable AEs.

n Pregnancy testing will also be performed whenever an expected menstrual cycle is missed or when pregnancy is otherwise suspected.

9.0 TRIAL PROCEDURES

The Trial Flow Chart - Section 8.0 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.

9.1 Administrative Procedures

9.1.1 Informed Consent

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

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

A copy of the signed and dated consent form should be given to the subject before participation in the trial.

The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the subject must receive the IRB/ERC's approval/favorable opinion in advance of use. The subject or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the subject's dated signature or by the subject's legally acceptable representative's dated signature.

The informed consent will adhere to IRB/ERC requirements, applicable laws and regulations and Sponsor requirements.

9.1.2 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.

9.1.3 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.

9.1.4 Prior and Concomitant Medications Review

9.1.4.1 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.

9.1.4.2 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.

9.1.5 Disease Details and Treatments

9.1.5.1 Disease Details

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

9.1.5.2 Prior Treatment Details

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

9.1.5.3 Subsequent Anti-Cancer Therapy Status

The investigator or qualified designee will review all new anti-neoplastic therapy initiated after the last dose of trial treatment. If a subject initiates a new anti-cancer therapy within 30 days after the last dose of trial treatment, the 30 day Safety Follow-up visit must occur before the first dose of the new therapy. Once new anti-cancer therapy has been initiated the subject will move into survival follow-up.

9.1.6 Assignment of Screening Number

After signing consent, each subject will be assigned a screening number that will then serve as the study ID for the duration of the study, if the patient is deemed eligible and enrolled to the study.

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

The investigator or qualified designee will review the subject's compliance with vorinostat dosing and administration and collect the subject's vorinostat diary on day 1 of each cycle.

9.2 Clinical Procedures/Assessments

9.2.1 Adverse Event (AE) Monitoring

The investigator or qualified designee will assess each subject to evaluate for potential new or worsening AEs as specified in the Trial Flow Chart and more frequently if clinically indicated. Adverse experiences will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE Version 4.03. Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

9.2.2 Adverse Event (AE) collection guidelines

- During Cycles 1-2, all grade toxicities with start and stop dates will be reported in the eCRFs.
- After Cycle 2 until the end of the safety follow-up period (30-days post-last dose for AE or 90 days post-last dose for SAE), the highest grade toxicity per cycle and the highest grade toxicity and all SAEs during the safety follow-up period with start/stop dates will be reported in the eCRFs.

9.2.3 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.

9.2.4 Vital Signs

The investigator or qualified designee will take vital signs at screening, prior to the administration of each dose of trial treatment and at treatment discontinuation as specified in the Trial Flow Chart (Section 8.0). Vital signs should include temperature, pulse, respiratory rate, weight, blood pressure, and oxygen saturation. Height will be measured at screening only.

9.2.5 Eastern Cooperative Oncology Group (ECOG) Performance Scale

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

9.2.6 Tumor Imaging and Assessment of Disease

Disease response/progression will be evaluated using the 2014 Lugano Classification (see Appendix C) [122, 139]. Participants who meet the definition of progressive disease per Lugano Classification should be evaluated using the LYRIC criteria (see Appendix L).

For all patients:

- Disease staging will be performed every 4 cycles until disease progression or off study therapy.
- Disease assessment will be performed either by PET-CT (FDG-avid histologies) or diagnostic quality CT of the neck, chest, abdomen and pelvis (N/C/A/P) with IV contrast (see restrictions below).
- MRI may be performed at the investigator's discretion for lesions not well-visualized by CT, or if CT with intravenous contrast is contraindicated.
- Whenever a PET-CT is not performed, a diagnostic quality (N/C/A/P) CT with IV contrast must be performed instead.
  Note: if there is no evidence of neck involvement by lymphoma at baseline, CT of chest, abdomen and pelvis (C/A/P) can be performed instead of N/C/A/P at subsequent re-staging.

For DLBCL and HL patients only:

- Disease assessment requires a PET-CT be performed at baseline (within the screening window) and at cycle 4 (Day 15-21 [-3 days]).
- Although not required, it is recommended that DLBCL and HL patients who are not in CR get a PET-CT at least every 8 cycles thereafter, and every 24 weeks for patients who discontinued for other reasons than CR.
- Assessment with PET-CT is required to confirm CR. Once CR has been confirmed, diagnostic quality (N/C/A/P) CT with IV contrast can be used instead of PET-CT until progression, unless otherwise specified below.
  Note: if there is no evidence of neck involvement by lymphoma at baseline, CT of chest, abdomen and pelvis (C/A/P) can be performed instead of N/C/A/P at subsequent re-staging.

For FL patients only:

- Disease assessment by diagnostic quality (N/C/A/P) CT with IV contrast or PET-CT is allowed at any time point.
  Note: if there is no evidence of neck involvement by lymphoma at baseline, CT of chest, abdomen and pelvis (C/A/P) can be performed instead of N/C/A/P at subsequent re-staging.

PET-CT and CT results will be read by radiology at each study site and investigator response based on radiology reading will be performed. Lymphoma response assessment based on PET-CT/CT will be based on the 2014 Lugano Classification (Appendix C).[139]

Unless clinically indicated, bone marrow aspirate and biopsy need only to be performed to confirm CR in patients with bone marrow involvement at study enrollment.

For patients with progression of disease on imaging, it is strongly recommended that a confirmatory biopsy be obtained whenever possible. Note that an FDG-negative PET scan will only be considered complete remission in patients whose tumor was FDG-avid at baseline.

9.2.6.1 Disease Progression Assessments

Response patterns observed with immunotherapeutic agents such as pembrolizumab may extend beyond the typical time course of responses seen with cytotoxic agents, and can manifest a clinical response after an initial increase in tumor burden or even the appearance of new lesions. Standard response criteria may not provide a complete response assessment of immunotherapeutic agents like pembrolizumab. Therefore, at a scheduled disease assessment, if the assessment demonstrates PD, the study regimen may be continued, at the discretion of the principal investigator, until the next disease response assessment provided that the subject's clinical condition is stable and the conditions below are met. However, imaging should occur at any time where there is clinical suspicion of progression.

Subjects may continue to receive treatment in the event of progressive disease if the following criteria are met:

- Absence of signs or symptoms (including worsening of laboratory values) indicating disease progression.
- No decline in ECOG performance status.
- Absence of rapid progression of disease
- Absence of progressive tumor at critical anatomical sites (e.g. spinal cord compression) requiring urgent alternative medical intervention.

At disease response assessments beyond the initial assessment, the Investigator, in consultation with the Principal Investigator, may keep a clinically stable subject on study treatment as long as the subject meets the above criteria and is deriving clinical benefit.

9.3 Tumor Tissue Collection

Each subject will have tumor tissue collected from either a standard of care fresh core or excisional biopsy of a tumor lesion prior to starting study therapy or will have available archival tissue from a biopsy that was performed after the most recent systemic therapy. All participants will have bone marrow (BM) aspirate performed at baseline (unless performed -within window specified and -meeting requirements specified in study calendar (footnote j) prior to consent as standard of care) except HL patients for who a screening bone marrow biopsy is not required (but can be performed for staging purposes at investigator discretion). Subjects with bone marrow involvement at baseline will have a bone marrow biopsy to confirm CR. It is recommended that progression of disease be confirmed by biopsy, if feasible, and fresh or archival tissue should be collected from that tumor biopsy for research purposes.

9.3.1 Tumor tissue handling guidelines

9.3.1.1 Guidelines for paraffin-embedded specimens

Using the formalin-fixed paraffin embedded (FFPE) tissue block, the following samples will be processed for correlative studies:

- If tissue block is available submit:
  - 6 paraffin scrolls measuring 10 μm thick placed into a Nunc tube and frozen at -80° C AND
  - 10 x 5 micron unstained slides
- If tissue block is unavailable submit 20 x 5 μm unstained slides
  - 5 of these unstained slides will be processed according to the QualTek Sample Handling Manual.

Note: For FL patients only (both escalation and expansion cohort): COH will submit a subset of tumor tissue (scrolls or slides) to the Jackson Laboratory for ctDNA analysis (upon sample receipt for non-COH sites). Refer to COH clinical study protocol #17072 for details and to Appendix E for tissue shipping guidelines.

9.3.1.2 Guidelines for fresh tumor tissue processing

Three core biopsies OR excisional biopsies should be submitted. If fewer than 3 core biopsies are available because of safety, then 1 or 2 cores may be submitted.

Core biopsies:

Three core biopsies will be obtained for diagnostic purposes and 3 similar additional cores will be obtained for research.

The research portion of the specimen (banking):

- One core biopsy will be snap frozen in OCT fixative, and an additional half of a core will be snap frozen without OCT fixative.
- Half of a core will be finely minced in a 10cm petri dish and frozen at -80° C in a Nunc tube in 1 ml of RPMI-1640 medium containing 20% fetal calf serum and 10% DMSO, then will be transferred to liquid nitrogen.
- Half of a core will be processed for DNA and RNA extraction according to the manufacturer's recommendation.
- The final half of a core biopsy will be processed to dissociate the cells, with the cell suspension cryopreserved in liquid nitrogen.

Excisional biopsies:

- An approximately 1cm x 1cm tumor sample will be divided into 5 equal portions and processed as described for core biopsies.

The diagnostic portion of the specimen:

- Process in a routine fashion by hematopathology. Using the formalin-fixed paraffin embedded (FFPE) tissue block, 15 x 5 micron unstained slides will be obtained
  - 5 of these unstained slides will be processed according to the QualTek Sample Handling Manual.

Bone marrow specimens:

- 5 cc of bone marrow aspirate will be sent to the City of Hope CICSL for processing and storage according to instructions in the laboratory manual.
- 10 x 5 micron unstained slides
- 5 of these unstained slides will be processed according to the QualTek Sample Handling Manual.

9.3.1.3 Labeling of samples

Samples will be labeled with the study number, subject ID (issued by DCC), date, time point of collection (i.e. baseline or progression) and if applicable patient initials.

9.3.1.4 Sample shipment and receiving lab

Tissue specimens collected at the above indicated time points will be taken to COH Pathology Core. Please include the **Correlative Tissue form (Appendix J)**.

9.4 Correlative Studies Blood Sampling

9.4.1 Overview and Timepoints

Peripheral blood (PB) will be collected for additional correlative studies prior to study treatment on day 1 of cycles 1 and 2, and 5, and every 4 cycles thereafter. Refer to Table 9 for details.

Table 9. Overview of correlative blood studies

Time points of collection	Total volume collected	Tube type	Receiving laboratory		Type of analysis (non-exhaustive)
			HL and DLBCL patients	FL patients	
C1D1, C2D1, C5D1	20 ml	Green-top (sodium or lithium heparin)	APCF	APCF	FACS
C1D1, C2D1, C5D1, and every 4 cycles thereafter and at discontinuation	20 ml	Purple-top (K+EDTA) **(For all COH patients except FL)** **OR** Cell-free DNA BCT® (Streck) **(For all COH FL patients)**	APCF	JAX	ctDNA/MRD

Sites should request Cell-free DNA BCT® (Streck) for FL patients from Dr. Honey Reddi or designee (Honey.Reddi@jax.org). For DLBCL and HL patients, sites should request tubes from the COH Data Coordinating Center (DCC). Contact information: E-mail: DCC@coh.org.
APCF = Analytical Pharmacology Core Facility (COH).
JAX = The Jackson Laboratory.

9.4.2 Labeling of blood samples

Label tubes with COH protocol #, subject ID (issued by DCC), date and timepoint of collection (e.g. C1D1 for Day1 of Cycle 1), and if applicable patient initials.

9.4.3 Blood collection

Before scheduled blood collection (at least one day in advance) e-mail Leslie Smith-Powell (LSmith-Powell@coh.org) or Stephanie Lee (stlee@coh.org) at the Analytical Pharmacology Core Facility (APCF) to inform them of a pending collection.

Refer to Table 10 for collection and post-collection instructions.

Note: Collection of blood in Cell-free DNA BCT® (Streck) or purple tubes has priority over the collection of blood in green-top tubes. Also, any heparin in the collection tube of the line used to draw the blood in purple tube will make it unusable.

Table 10. Blood sample collection and post-collection instructions.

Tube Type	Collection details	Site of collection	Post-collection instructions	
			HL and DLCBL patients	FL patients
Green-top	1- Blood samples will be collected from an indwelling venous catheter or by venipuncture. 2- Invert tubes eight times after collection. 3- **Immediately** place the tubes on **ice**.	COH	**Promptly** deliver the blood samples on ice to the APCF, Shapiro room 1042 for processing **within 4 hours**.	Same as for HL and DLBCL patients
Purple-top	Same as for green-top.	COH Only	**Promptly** deliver the blood samples on ice to the APCF, Shapiro room 1042 for processing **within 4 hours**.	N/A
Cell-free DNA BCT® (Streck)*	1- If applicable, follow recommendations for order of draw outlined in CLSI GP41-A6**. 2- Blood samples will be collected from an indwelling venous catheter or by venipuncture. **Prevention of backflow:** *(Since cell-free DNA BCT® contain chemical additives)* a. Keep patient's arm in the downward position during the collection procedure. b. Hold the tube with the stopper in the uppermost position so that the tube contents do not touch the stopper or the end of the needle during sample collection. c. Release tourniquet once blood starts to flow in the tube, or within 2 minutes of application. 3- Fill tube completely. 4- Remove tube from adapter and immediately mix by gentle inversion 8 to 10 times. 5- **Do not freeze** samples. Store samples at 18-25^{o}C until shipment.	COH	N/A	Ship samples to JAX (see Appendix I). Refer to COH clinical study protocol #17072 for details.

* Tubes are stable when stored at 2-30^{0}C through expiration date. Do not use expired tubes. If there is any indication of cloudiness or visible precipitate immediately contact: (1) For FL patients, Dr. Honey Reddi or designee (Honey.Reddi@jax.org), any unused/expired blood collection kits should be returned to the Jackson Laboratory Laboratory. (2) For DLBCL and HL patients, contact the COH Data Coordinating Center. Contact information: E-mail: DCC@coh.org.

** Additional guidelines: Cell-Free DNA BCT should be drawn after the EDTA tube and before the fluoride oxalate (glycolytic inhibitor) tube. If a Cell-Free DNA BCT tube immediately follows a heparin tube in the draw order, Streck recommends collecting a non-additive or EDTA tube as a waste tube prior to collection in the Cell-Free DNA BCT tube.

9.4.4 Sample Processing by APCF (COH)

COH samples only: Blood samples will be kept on a rocker set at low speed to mimic circulation and avoid clot formation until processing.

Green-top tubes (PBMCs AND plasma), for FACS/Cytokine assays:

(Process within 4h of collection for COH samples OR upon receipt of non-COH samples).

- Centrifuge for 10 min at 1800g at 4ºC. Both supernatant and pellet will be used.

- Plasma:

  - The resulting upper plasma layer from each tube will be drawn up sequentially into a sterile 5 mL syringe and pushed through a sterile 0.2/0.8 micron disposable filter.

  - The filtered plasma will then be transferred in 500 µL aliquots into multiple appropriately-labeled Starstedt microfuge tubes.

  - To one aliquot, add 0.5 mL glycerol/0.02% sodium azide solution to dilute the plasma 50/50 v/v. Keep the diluted plasma sample at -20˚C and do not freeze.

  - All the remaining plasma aliquots will be stored frozen at -80˚C until ready for testing.

- PBMCs:

  - Dilute the blood remaining in the green-top tubes used to prepare plasma above 1:1 with Hank's Balanced Salt Solution (or equivalent) in a sterile conical centrifuge tube.

  - Isolate PBMCs by Ficoll-gradient separation per COH APCF procedures.

  - PBMCs samples will be stored in liquid nitrogen until use.

9.5 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial, including laboratory tests for hematology, chemistry, urinalysis, and others are specified in Table 11.

Table 11. Laboratory Tests

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

† 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.

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.

9.5.1 Correlative Studies

A non-exhaustive list of correlative studies is provided in Section 4.6.5 "Rationale for Biomarker Research".

Correlative studies will mainly be performed in the laboratories of Peter Lee, MD, Chair of the City of Hope Beckman Research Institute Division of Cancer Immunotherapeutics and Tumor Immunology, and John Chan, MD, Professor of Pathology at City of Hope Medical Center.

For FL patients only, some tumor and blood samples will be analyzed at the Jackson Laboratory (ctDNA studies) (see COH clinical study protocol #17072).

9.5.2 Other Procedures

9.5.2.1 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 that are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 9.2. Subjects who a) attain a CR or b) complete 24 months of treatment with pembrolizumab may discontinue treatment. After discontinuing treatment following assessment of CR or completing 24 months of treatment, these subjects should return to the site for a Safety Follow-up Visit and then proceed to the Follow-Up Period of the study.

9.5.3 Visit Requirements

Visit requirements are outlined in Section 8.0 - Trial Flow Chart. Specific procedure-related details are provided above in Section 9.0 - Trial Procedures.

9.5.3.1 Screening Period

<u>The following procedures will be performed during Screening:</u>

- Informed Consent
- Review of eligibility criteria (Inclusion/Exclusion criteria)
- Medical history and demographics
- Review of prior and concomitant medications

- Complete physical exam
- Vital signs, weight and height, and oxygen saturation
- ECOG Performance Status
- 12-lead ECG
- Bone marrow aspirate and biopsy (Not for all patients: refer to study calendar and footnote j).
- Collection of tumor tissue from fresh tumor biopsy or archival specimen
- PET-CT (DLBCL, HL, FL) or IV contrast-enhanced CT scan of neck, chest, abdomen, pelvis of diagnostic quality (only FL). MRI can be used for lesions not well-visualized by CT, or if CT with IV contrast is contraindicated. See sections 9.2.6 and 10.1 for additional details.
- Clinical laboratory tests for:
    - Hematology
    - Serum chemistry
    - Coagulation (PT, PTT, INR)
    - Serum or urine pregnancy test (for women of childbearing potential who have not been free from menses for > 1 year). Should be performed within 72 hours prior to first dose of therapy.
    - Urinalysis

9.5.3.2 Treatment Period

The following procedures will be performed during the treatment period:

NOTE: This is a list of procedures. Not all procedures will necessarily be performed at each cycle.

- Complete physical exam
- ECOG Performance Status
- Vital signs and weight

- Buccal swab
- 12-lead ECG
- Clinical laboratory tests for:
    - Hematology
    - Serum chemistry
    - Thyroid function panel
    - Serum or urine pregnancy test (for women of childbearing potential who have not been free from menses for > 1 year).
- Review of AEs
- Research laboratory blood samples collected pre-dose for correlative studies (See section 9.4 for additional details).
- PET-CT or IV contrast-enhanced CT scan of neck, chest, abdomen, pelvis of diagnostic quality. See sections 9.2.6 and 10.1 for additional details.
- To be completed to confirm CR:
    - PET scan (if only CT scan was used for response assessment)
    - Bone marrow aspirate and biopsy (if bone marrow was involved at baseline)
- Dosing
    - Dispense vorinostat and diary card
    - In-clinic administration of vorinostat
    - In-clinic administration of pembrolizumab (after vorinostat administration)

9.5.3.3 Post-Treatment Visits

9.5.3.3.1 Safety Follow-Up Visit

The mandatory Safety Follow-Up Visit should be conducted 30 days after the last dose of trial treatment or before the initiation of a new anti-cancer treatment, whichever comes first. 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.

9.5.3.4 Follow-up Visits

Subjects who discontinue trial treatment for a reason other than disease progression will move into the Follow-Up Phase and should be assessed every 12 weeks (84 ± 7 days) by radiologic imaging to monitor disease status. After 1 year, the imaging time point will occur every 18 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, and end of the study. Information regarding post-study anti-neoplastic treatment will be collected if new treatment is initiated.

9.5.3.4.1 Survival Follow-up

Once a subject experiences confirmed disease progression or starts a new anti-cancer therapy, the subject moves into the survival follow-up phase and will be followed for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first. Survival assessment to occur bi-annually or as requested by the Study PI via medical record review, review of social security registry, or telephone call.

10.0 ENDPOINT EVALUATION CRITERIA/MEASUREMENT OF EFFECT

10.1 Response Criteria

Disease response/progression will be evaluated using 2014 Lugano Classification (see Appendix C)[122, 139]. Participants who meet the definition of progressive disease per Lugano Classification should be evaluated using the LYRIC criteria (see Appendix L).

For all patients:

- Disease staging will be performed every 4 cycles until disease progression or off study therapy.
- Disease assessment will be performed either by PET-CT (FDG-avid histologies) or diagnostic quality CT of the neck, chest, abdomen and pelvis (N/C/A/P) with IV contrast (see restrictions below).
- MRI may be performed at the investigator's discretion for lesions not well-visualized by CT, or if CT with intravenous contrast is contraindicated.
- Whenever a PET-CT is not performed, a diagnostic quality (N/C/A/P) CT with IV contrast must be performed instead.

  Note: if there is no evidence of neck involvement by lymphoma at baseline, CT of chest, abdomen and pelvis (C/A/P) can be performed instead of N/C/A/P at subsequent re-staging.

For DLBCL and HL patients only:

- Disease assessment requires a PET-CT be performed at baseline (within the screening window) and at cycle 4 (Day 15-21 [-3 days]).
- Although not required, it is recommended that DLBCL and HL patients who are not in CR get a PET-CT at least every 8 cycles thereafter, and every 24 weeks for patients who discontinued for other reasons than CR.
- Assessment with PET-CT is required to confirm CR. Once CR has been confirmed, diagnostic quality (N/C/A/P) CT with IV contrast can be used instead of PET-CT until progression, unless otherwise specified below.
  Note: if there is no evidence of neck involvement by lymphoma at baseline, CT of chest, abdomen and pelvis (C/A/P) can be performed instead of N/C/A/P at subsequent re-staging.

For FL patients only:

- Disease assessment by diagnostic quality (N/C/A/P) CT with IV contrast or PET-CT is allowed at any time point.
  Note: if there is no evidence of neck involvement by lymphoma at baseline, CT of chest, abdomen and pelvis (C/A/P) can be performed instead of N/C/A/P at subsequent re-staging.

PET-CT and CT results will be read by radiology at each study site and investigator response based on radiology reading will be performed. Lymphoma response assessment based on PET-CT/CT will be based on the 2014 Lugano Classification (Appendix C).[139]

Unless clinically indicated, bone marrow aspirate and biopsy will be performed only to confirm CR and only in patients with bone marrow involvement at study enrollment.

For patients with progression of disease on imaging, it is strongly recommended that a confirmatory biopsy be obtained whenever possible. Note that an FDG-negative PET scan will only be considered complete remission in patients whose tumor was FDG-avid at baseline.

As a secondary endpoint, we will evaluate the LYRIC refinement of the Lugano classification (Appendix L), which is specifically aimed at improving response evaluation in lymphoma immunotherapy clinical trials.[28]

10.2 Endpoint Definitions

Overall Response Rate (ORR): Defined as the proportion of patients that have a documented CR or PR at any time during study treatment.

Complete Response (CR) rate: Defined as the proportion of patients that have a documented CR at any time during study treatment.

Duration of Response (DOR): Defined as the time from the first achievement of PR or CR to time of PD. Patients who never achieve PR or CR are excluded. Patient who has not had disease progression/relapse at last follow-up is censored at the time of last follow-up. If a patient receives non-protocol anti-lymphoma treatment prior to disease progression, the patient is censored at the time of non-protocol anti-lymphoma treatment.

Overall Survival: Defined as time from initiation of study therapy to death from any cause. If a patient is alive at the last evaluation time period, survival time is censored at the time of last follow-up.

Progression-Free Survival (PFS): Defined as the time from initiation of study therapy to the first observation of disease relapse/progression or death from any cause, whichever occurs first. If the patient has not progressed relapsed or died, the patient is censored at the time of last follow-up. If a patient receives non-protocol anti-lymphoma treatment prior to disease progression, the patient is censored at the time of non-protocol anti-lymphoma treatment.

Toxicity: Toxicity and adverse events will be recorded using the NCI CTCAE 4.03 scale. Observed toxicities will be summarized by type (organ affected or laboratory determination such as absolute neutrophil count), severity (by NCI CTCAE v4.03 and nadir or maximum values for lab measures), date of onset, duration, reversibility, and attribution.

Unacceptable Toxicity: defined as one of the following AEs that is at least possibly related to study treatment, at any point on study therapy:

- Any Gr 3 or higher IrAE that does not resolve to Gr ≤1 within 7 days with the exception of:
    - Grade 3 immune-related hepatitis if ALT or AST < 8 x ULN or total bilirubin < 5 x ULN.
    - Grade 3 asymptomatic endocrinopathy.
    - Local inflammatory response to study therapy.
- Any other Gr ≥4 AE with the exception of:
    - Non-clinically significant laboratory abnormalities
    - Local inflammatory response to study therapy.
- Any Gr 5 AE.

11.0 STATISTICAL ANALYSIS PLAN

11.1 Statistical Analysis Plan

11.1.1 Demographic and Baseline Characteristics

Patient demographic and baseline characteristics, including age, gender, medical history, and prior therapy, will be summarized using descriptive statistics. For continuous variables, descriptive statistics (number [n], mean, standard deviation, standard error, median (range) will be provided. For categorical variables, patient counts and percentages will be provided.

11.1.2 Toxicity Analysis

Observed toxicities will be summarized by type (organ affected or laboratory determination such as absolute neutrophil count), severity (by NCI CTCAE v4.03 and nadir or maximum values for lab measures), date of onset, duration, reversibility, and attribution.

11.1.3 Analysis of Anti-tumor Activity

This study will aim to obtain preliminary estimates of the anti-tumor activity of the study combination. ORR will be calculated as the proportion of evaluable patients that have confirmed CR or PR, as defined according to the 2014 Lugano Classification, exact 95% confidence intervals will be calculated for these estimates. Response rates will also be evaluated based on number and type of prior therapy(ies). Time to response, duration of response, as well as progression-free survival and overall survival will be estimated using the product-limit method of Kaplan and Meier.

These efficacy analyses will be performed separately for DLBCL, FL, and HL patients. Any patient treated at the RP2D, including those from the dose-escalation cohort, will be included in efficacy analyses. Patients will be evaluable for efficacy assessment if they received at least one dose of vorinostat and one dose of pembrolizumab and underwent at least one response assessment. Patients will be evaluable for efficacy if they discontinued study therapy prior to the first response assessment because of progression of disease rather than solely because of unacceptable toxicity, withdrawal of consent, or investigator decision. If a patient discontinues study treatment prior to the first response assessment due to progressive disease, the treating physician is encouraged to obtain imaging to confirm progression.

11.2 Safety Analysis and Stopping Rules for Excessive Toxicity in the Expansion Cohort

During enrollment into the expansion cohort, toxicity information recorded will include the type, severity, and the probable association with the study regimen. Tables will be constructed to summarize the observed incidence by severity and type of toxicity.

Because of the unique immune-related adverse events (IrAEs) observed with checkpoint inhibitors, we will monitor for “unacceptable toxicity” with this new combination of drugs

(defined in Section10.2). The expected rate of "unacceptable toxicity" should not be ≥33%. The early stopping rule for unacceptable toxicity will be assessed after enrollment of 12 patients (total, across cohorts) treated at the RP2D and will be assessed once the 12th patient has completed at least 4 cycles of therapy. If >3 "unacceptable toxicity" events occur in the first 12 patients (≥33%) treated (across disease subtypes) at RP2D, or at a rate ≥33% anytime thereafter at the quarterly review, accrual will be halted and a full review of these events will be performed by the City of Hope Data Safety Monitoring Committee (DSMC). Patient accrual will not resume until approved by the DSMC to do so. These rules are in addition to the quarterly review of all toxicities submitted to the City of Hope Data Safety Monitoring Committee (DSMC). Patients with ongoing toxicity will be followed until resolution or stability.

11.3 Sample Size Accrual Rate

The expected sample size is 52 evaluable patients: 12 during the dose-escalation portion, and 40 patients in the expansion cohort. The minimum sample size is 6 evaluable patients. Patients evaluable/inevaluable for dose-escalation portion and for dose expansion cohort are defined in Section 7.4 and 11.1.3 respectively. Considering replacement of inevaluable patients, the maximum study accrual is set at 60 patients.

11.4 Correlative Studies

A non-exhaustive list of correlative studies is provided in Section 4.6.4.3 "Biomarker Research". These studies are exploratory in nature and meant to be hypothesis-generating.

Genomic Correlative Analyses: Comprehensive genomic analyses (i.e., WES and GEP) will be performed on pre-treatment tumor samples. We will: 1) quantify and compare total exonic mutational load between responders and non-responders; 2) assess association between mutational load and PFS; 3) assess individual genetic alterations for association with response and PFS; 4) compare GEP between responders and non-responders and assess association with PFS.

Statistical Considerations: Total exonic mutational load (TEML) will be quantified for each subject using the pre-treatment samples; these measures will be summarized within and across histology-based cohorts. Wilcoxon rank sum tests will be used to compare TEML levels between two groups, and Fisher exact tests to compare incidence of specific mutations between groups. In addition, logistic regression models will be used to evaluate the influence of TEML on whether or not patients responded to therapy. For HL patients, we will evaluate influence of TEML on achievement of CR, assuming that approximately 30% will achieve CR. We will also evaluate the TEML on achievement of CR or PR for at least 6 months. For the DLBCL and FL cohorts, we will evaluate each for the influence of TEML on achievement of response (~40-50%) using logistic regression analyses. For each of these cohorts, we will also assess the influence of TEML on PFS using Cox regression models and log-rank tests. Multivariable versions of these models will also be used to adjust for other clinical characteristics. Similar analyses will be used for evaluating the influence of specific mutations (dichotomized

measures) as well as GEP. We will use a log2 transformation of the GEP measures in our analyses, following standard practice for these types of expression measures. We will also evaluate the influence of immunologic markers on response and PFS for these different histology groups in a similar manner. Spatial markers will be assessed via a density measure of the different immune cell subsets and checkpoint molecules. Finally, we will also assess if there are meaningful cut-points for the TEML and other continuous measures that correspond with response or PFS using recursive partitioning algorithms. The influence of these resulting dichotomized markers will then be assessed in relation to the corresponding clinical outcomes.

Quantitative PET analyses: Quantitative PET parameters and their change over time will be summarized by various descriptive statistics. We will explore their association with clinical endpoints (complete response, overall response and PFS) using appropriate statistical tests (such as two-sample t-test and Wilcoxon rank sum test for analyses on response and log rank test for analyses on PFS) and regression analyses (logistic regression for response and Cox proportional hazards model for PFS).

12.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

12.1 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 12.

Table 12. Product Descriptions

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

12.2 Packaging and Labeling Information

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

12.3 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.

12.4 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.

12.5 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.

13.0 STUDY OVERSIGHT, QUALITY ASSURANCE, AND DATA & SAFETY MONITORING

13.1 Site Lead Investigator Responsibilities

The Site Lead Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations (CFR). The Site Lead Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

It is the responsibility of the Site Lead Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events, deviations, and unanticipated problems.

The Site Lead Investigator will be responsible for assuring that all the required data will be collected and entered onto the Case Report Forms at his/her site. For remote or onsite monitoring and auditing, the Site Lead Investigator will provide access to his/her original

records to permit verification of proper entry of data. At the completion of the study, all case report forms will be reviewed by the Site Lead Investigator and will require his/her final signature to verify the accuracy of the data.

An investigator is responsible for ensuring that an investigation is conducted according to the signed investigator statement, the investigational plan, and applicable regulations; for protecting the rights, safety, and welfare of participants under the investigator's care; and for the control of drugs under investigation.

13.2 All Investigator Responsibilities

All investigators agree to:

- Conduct the study in accordance with the protocol and only make changes after notifying the Sponsor (or designee), except when necessary to protect the safety, rights or welfare of subjects.
- Personally conduct or supervise the study (or investigation).
- Ensure that the requirements relating to obtaining informed consent and IRB review and approval meet federal guidelines, as stated in § 21 CFR, parts 50 and 56.
- Report to the Sponsor or designee any AEs that occur in the course of the study, in accordance with §21 CFR 312.64.
- Ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments.
- Maintain adequate and accurate records in accordance with §21 CFR 312.62 and to make those records available for inspection with the Sponsor (or designee).
- Ensure that an IRB that complies with the requirements of §21 CFR part 56 will be responsible for initial and continuing review and approval of the clinical study.
- Promptly report to the IRB and the Sponsor all changes in the research activity and all unanticipated problems involving risks to subjects or others (to include amendments and IND safety reports).
- Seek IRB and Sponsor approval before any changes are made in the research study, except when necessary to eliminate hazards to the patients/subjects.
- Comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements listed in § 21 CFR part 312.

13.3 Study PI Responsibilities

The Study PI is responsible for the conduct of the clinical trial, including overseeing that sponsor responsibilities as defined in § 21 CFR 312.

13.4 Protocol Management Team (PMT)

The PMT minimally consisting of the Study Principal Investigator, collaborating investigators, the research nurse, the clinical research associate/coordinator, and the study biostatistician is responsible for ongoing monitoring of the data and safety of this study.

The PMT will meet (in person or via teleconference) at least monthly, and will meet at least quarterly with the study biostatistician, to review study status. This review will include, but not be limited to, reportable AEs and UPs, and an update of the ongoing study summary that describes study progress in terms of the study schema. The meeting will be a forum to discuss study related issues including accrual, SAE/AEs experienced, study response, deviations/violations and study management issues. The appropriateness of further subject enrollment and the specific intervention for subsequent subject enrollment are addressed, including the implementation of stopping rules.

13.5 Monitoring/ Auditing

Clinical site auditing/ monitoring is conducted to ensure that the rights of human subjects are protected, that the study is implemented in accordance with the protocol and regulatory requirements, and that the quality and integrity of study data and data collection methods are maintained. Monitoring for this study will be performed by the City of Hope Office of Clinical Trials Auditing and Monitoring (OCTAM).

The site Investigator/Institution will permit the study monitors and appropriate regulatory authorities direct access to the study data and to the corresponding source data and documents to verify the accuracy of this data. The Investigator will allocate adequate time for such monitoring activities. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the above noted study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit.

Details of clinical site monitoring are documented in the OCTAM SOP that is provided as a supplement to this document. This document specifies the frequency of monitoring, monitoring procedures, the level of clinical site monitoring activities (e.g., the percentage of subject data to be reviewed), and the distribution of monitoring reports. Staff from OCTAM will conduct monitoring activities and provide reports of the findings and associated action items in accordance with the details described in the SOP. Documentation of monitoring activities and findings will be provided to the study team, study PI, and the COH DSMC.

13.6 Quality Assurance

The City of Hope Clinical Research Information Support will provide quality assurance.

An additional level of quality assurance of the study-required images will be performed by the Study PI.

13.7 City of Hope Data and Safety Monitoring Committee (DSMC)

This is a Risk Level 4 study, as defined in the City of Hope Data and Safety Monitoring Plan because the trial involves a COH IND.

The DSMC is a multidisciplinary committee charged with overseeing the monitoring of safety of participants in clinical trials, and the conduct, progress, validity, and integrity of the data for

all clinical trials that are sponsored by City of Hope. The committee is composed of clinical specialists with experience in oncology and who have no direct relationship with the study. The committee reviews the progress and safety of all active research protocols that are not monitored by another safety and data monitoring committee or board.

The COH DSMC will review and monitor toxicity and accrual data from this trial. Information that raises any questions about participant safety will be addressed with the Principal Investigator, statistician and study team.

This study will utilize the Phase 1 Tracking Log to monitor data and safety for dose escalation. The Tracking Log will contain dose levels administered, dose limiting toxicities (DLT), DLT-defining adverse events, and any details regarding dose level escalation. The record of doses administered and resultant adverse events will be included in the PMT Report.

The DSMC will review the study's status per COH policies and/or more frequently if necessary. The DSMC will review up-to-date participant accrual; summary of all adverse events captured via routine and expedited reporting; a summary of deviations; any response information; monitoring reports, and summary comments provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request. A review of outcome results (response, toxicity and adverse events) and factors external to the study (such as scientific or therapeutic developments) is discussed, and the Committee votes on the status of each study.

Data and safety will be reported from the date of activation to the COH DSMC using the PMT report per COH policies.

14.0 ADVERSE EVENT AND UNANTICIPATED PROBLEM REPORTING

The authorized investigator will be responsible for determining the event name, assessing the severity (i.e., grade), expectedness, and attribution of all adverse events.

14.1 Definitions

- **Adverse Event (AE)** [Modified from the definition of adverse event in 21 CFR 312.32] - An adverse event is any untoward medical experience or change of an existing condition that occurs during or after treatment, whether or not it is considered to be related to the protocol intervention.
- **Serious Adverse Event (SAE)** [Modified from the definition of unexpected adverse drug experience in 21 CFR 312.32] - defined as any *expected or unexpected adverse events* that result in any of the following outcomes:
  - Death
  - Is life-threatening experience (places the subject at immediate risk of death from the event as it occurred)
  - Unplanned hospitalization (equal to or greater than 24 hours) or prolongation of existing hospitalization
  - A persistent or significant disability/incapacity
  - A congenital anomaly/birth defect

- Secondary malignancy
- Any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the outcomes listed above (examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias of convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

- **Adverse Event Description and Grade**
  - The description and grading scales found in the most recent version of CTCAE will be utilized to characterize AEs. AEs not covered by specific terminology listed should be reported with common medical terminology, and documented according to the grading scales provided in the CTCAE v 4.0. The NCI Common Terminology Criteria for Adverse Events (CTCAE) v. 4.0 will be utilized for AE grading. All appropriate treatment areas should have access to a copy of the CTCAE v. 4.0. A copy can be downloaded from the NCI/ CTEP web site.

- **Unexpected Adverse Event** – An adverse event is unexpected if it is not listed in the investigator's brochure and/or package insert; is not listed at the specificity or severity that has been observed; is not consistent with the risk information described in the protocol and/or consent; is not an expected natural progression of any underlying disease, disorder, condition, or predisposed risk factor of the research participant experiencing the adverse event. Modified from 21 CFR 312.32 (a).
- **Expected Adverse Event** - An adverse event is expected if it does not meet the criteria for an unexpected event, OR is an expected natural progression of any underlying disease, disorder, condition, or predisposed risk factor of the research participant experiencing the adverse event.
- **Adverse Event Attribution**

  The following definitions will be used to determine the causality (attribution) of the event to the study agent or study procedure.

  - **Unrelated –** The event is clearly related to other factors such as the participant's clinical state, other therapeutic interventions, or concomitant medications administered to the participant.
  - **Unlikely –** The event is doubtfully related to the investigational agent(s). The event was most likely related to other factors such as the participant's clinical state, other therapeutic interventions, or concomitant drugs.
  - **Possible –** The event follows a reasonable temporal sequence from the time of drug administration, but could have been produced by other factors such as the participant's clinical state, other therapeutic interventions, or concomitant drugs.
  - **Probable –** The event follows a reasonable temporal sequence from the time of drug administration, and follows a known response pattern to the study drug.

The event cannot be reasonably explained by other factors such as the participant's clinical state, therapeutic interventions, or concomitant drugs.

- **Definite** – The event follows a reasonable temporal sequence from the time of drug administration, follows a known response pattern to the study drug, cannot be reasonably explained by other factors such as the participant's condition, therapeutic interventions, or concomitant drugs, AND occurs immediately following study drug administration, improves upon stopping the drug, or reappears on re-exposure.

- **Unanticipated Problem (UP)** – Any incident, experience, or outcome that **meets all three** of the following criteria:
  - Unexpected (in terms of nature, severity, or frequency) given the following: a) the research procedures described in the protocol-related documents such as the IRB approved research protocol, informed consent document or Investigator Brochure (IB); and b) the characteristics of the subject population being studied; AND
  - Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcomes may have been caused by the drugs, devices or procedures involved in the research); AND
  - Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm) than previously known or recognized.

14.2 Events of Special Interest Requiring Expedited Reporting

14.2.1 Overdose

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

For purposes of this trial, an overdose of vorinostat is considered to be any dose more than the prescribed dose. No specific information is available on the treatment of overdose of vorinostat. There is no specific antidote for vorinostat overdose. In clinical studies, the highest total daily doses tested were 600 mg (once daily), 800 mg (400 mg twice daily) and 900 mg (300 mg three times daily). In four patients who took more than the recommended study dose (without exceeding the highest doses tested), no adverse experiences were reported. Patients should be advised not to make up missed doses. If a patient has an episode of emesis after taking vorinostat, patient should be instructed not to take an additional dose.

14.2.2 Pregnancies

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) that occurs during the trial.

Efforts must be made by the investigator to follow the outcome of pregnancy outcome per institutional policies.

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. If the new-born is healthy additional follow-up is not necessary.

Any pregnancy related event described above must be **reported to the Study PI/ DCC** immediately **within 24 hours of awareness** (see Section 14.4).

14.2.3 Abnormal Liver Function Tests

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.

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.

14.3 Routine AE Reporting Guidelines

AEs will be collected from the signing of informed consent until ending study participation. Routine AE reporting will occur via data entry into the study eCRF. AEs reported through expedited processes (e.g., reported to the IRB, FDA, etc.) must also be reported in routine study data submissions.

- AEs recorded in the CRF include:
  - All events considered unrelated, unlikely, possibly, probably or definitely related to protocol therapy
  - Any Grade 1-5 during the DLT period (cycles 1 and 2), highest grade after cycle 2 during each cycle and during the safety follow-up period.
  - All SAEs.

14.4 Expedited AE Reporting Guidelines

Each adverse event will be assessed to determine if it meets the criteria for expedited reporting. Adverse event reporting is to occur according to the site's specific IRB guidelines, and as outlined in this Section.

Table 14.4 indicates what events must be reported expeditiously.

Serious Adverse Events that require expedited reporting and unanticipated problems will be reported according to the approved City of Hope's Institutional policy via electronic submission in iRIS.

Table 14.4 Expedited Reporting Guidelines

Time point	What to report expeditiously
From the signing of the consent to study completion	All unanticipated problems
Screening up to Day 1 of protocol therapy	• Pregnancy and lactation • Any reason for not starting Day 1 of protocol therapy
For the time period beginning at treatment through 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier	• All SAEs regardless of relationship to protocol therapy, study procedure, underlying disease or concomitant treatment. • Death due to any cause other than progression of the cancer under study • All AEs that meet the definition of a UP • Overdose (Section 14.2.1) of either agent • Pregnancies and lactation (Section 14.2.2) • Abnormal liver function tests (Section 14.2.3).
For participants yet to initiate anti-cancer therapy: From Day 1 of therapy up to 120 days post-last pembrolizumab dose	Pregnancies and lactation (Section 14.2.2).
Post Safety follow-up to removal from study	All SAEs that are considered possibly, probably, or definitely related to pembrolizumab
Note: follow-up reports must be submitted for all events that require expedited reporting when the status of the event changes and until the resolution or stabilization of the event.	

- Reportable adverse events must be followed until the event is resolved, stabilized, or determined to be irreversible by the investigator; for ongoing reportable adverse events that are unrelated to protocol therapy, the follow-up period may end 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier.

14.5 Additional reporting requirements

The Study PI (or designee) will:

- For IND Sponsor reporting purposes only: Report to the FDA, (via COH Office of IND Development and Regulatory Affairs (OIDRA)) regardless of the site of occurrence, any SAE that meets the FDA's criteria for expedited reporting following the reporting requirements and timelines set by the FDA:

Serious Adverse Events meeting the requirements for expedited reporting to the Food and Drug Administration (FDA), as defined in 21 CFR 312.32, will be reported as an IND safety report using the MedWatch Form FDA 3500A for Mandatory Reporting.

The criteria that require reporting using the MedWatch 3500A are:

- Any unexpected fatal or life threatening adverse experience associated with use of the drug must be reported to the FDA no later than 7 calendar days after initial receipt of the information [21 CFR 312.32(c)(2)]
- Any adverse experience associated with use of the drug that is both serious and unexpected must be submitted no later than 15 calendar days after initial receipt of the information [21 CFR 312.32(c)(1)]
- Any follow-up information to a study report shall be reported as soon as the relevant information becomes available. [21 CFR 312.32(d)(3)]

The PI or designee will be responsible for contacting the Office of IND Development and Regulatory Affairs (OIDRA) at COH to ensure prompt reporting of safety reports to the FDA. OIDRA will assist the PI with the preparation of the report and submit the report to the FDA in accordance with the approved City of Hope's Institutional policy.

- Report to Merck using a MedWatch form, (via COH OIDRA) regardless of the site of occurrence, any expedited AEs **within 2 working days** of being aware of the event. The initial report will be as complete as possible and include an assessment of the causal relationship between the event and the study agent(s). Information not available at the time of the initial report will be documented on a follow-up report and submitted to Merck.

  The Merck protocol number will be included on expedited reports (or on the fax cover letter). A copy of the fax transmission confirmation of the expedited report to Merck will be retained with the patient records.

  Merck Global Safety
  Attn: Worldwide Product Safety
  Fax: (215) 993-1220

- Submit annually **within 60 days** (via COH OIDRA) of the anniversary date of when the IND went into effect, an annual report to the FDA which is to include a narrative summary and analysis of the information of all FDA reports within the reporting interval, a summary report adverse drug experiences, history of actions taken since the last report because of adverse drug experiences.
- Forward to Merck (via COH OIDRA) a copy of the FDA Annual Progress Report at the time of submission to the FDA.

- Report to the COH DSMC a Protocol Management Team (PMT) report per frequency stated in COH policies, to include aggregate analysis of safety information and accrual and participant status.
- Report to Merck aggregate safety information at the time of COH DSMC PMT report.

15.0 DATA HANDLING, DATA MANAGEMENT, RECORD KEEPING

15.1 Source Documents

Source documents are original documents, data, and records (e.g., medical records, pharmacy dispensing records, recorded data from automated instruments, laboratory data) that are relevant to the clinical trial. The Site Investigator or their designee will prepare and maintain adequate and accurate source documents. These documents are designed to record all observations and other pertinent data for each patient enrolled in this clinical trial. Source documents must be adequate to reconstruct all data transcribed onto the case report forms.

15.2 Data Capture Methods and Management

Data for this trial will be collected using Medidata RAVE, City of Hope's electronic capture system. Medidata RAVE is a web based, password protected system that is fully compliant with global regulatory requirements, including 21CRF Part 11 compliant.

15.3 Case Report Forms/ Data Submission Schedule

Study personnel at each site will enter data from source documents corresponding to a participant's visit into the protocol-specific electronic Case Report Form (eCRF) when the information corresponding to that visit is available.

The investigator is responsible for all information collected on participants enrolled in this study. All data collected during the course of this study must be reviewed and verified for completeness and accuracy by the investigator. All case report forms must be completed by designated study personnel. The completed case report forms must be reviewed, signed and dated by the Site Investigator or designee in a timely fashion.

All data will be collected using electronic data collection system described in Section 15.2, and will be submitted according to the timelines indicated in Table 14.

Table 14. Data Submission Schedule

Form	Submission Timeline
Eligibility Checklist	Complete prior to registration
On Study Forms	Within 14 calendar days of registration
Baseline Assessment Forms	Within 14 calendar days of registration
Treatment Forms	Within 14 calendar days of treatment administration
Adverse Event Report Forms	Cycle 1 and 2: Within 7 calendar days of the assessment/notification Cycle 3+: Within 10 calendar days of the assessment/notification
Response Assessment Forms	Within 10 calendar days of the response assessment
Other Assessment Forms	Within 10 calendar days of the assessment

Form	Submission Timeline
Off Treatment/Off Study Forms	Within 10 calendar days of completing treatment or being taken off study for any reason
Follow up/ Survival Forms	Within 14 calendar days of the protocol defined follow up visit date or call

15.4 Regulatory Records

The investigator will maintain regulatory records, including updating records in accordance with Good Clinical Practice guidelines and FDA regulations.

16.0 ADHERENCE TO THE PROTOCOL

A deviation is a divergence from a specific element of a protocol that occurred without prior IRB approval.

It is understood that deviations from the protocol should be avoided, except when necessary to eliminate an immediate hazard to a research participant. Protocol deviations may be on the part of the participant, the investigator, or study staff.

All deviations from the protocol must be documented in study participant source documents and promptly reported to the Study PI and to the local IRB according to its policies requirements. The Study PI will report the deviation according to City of Hope's deviation policy for reporting deviations.

16.1 Definitions

16.1.1 Unplanned deviations

- **Emergency Modifications**

Investigators may implement a deviation from the protocol to eliminate an immediate hazard(s) for the protection, safety, and well-being of the study patient to trial participants without prior IRB or Sponsor approval.

- **Deviations Discovered After They Have Occurred**

Unplanned deviations from the protocol must be documented in study subject source documents.

16.1.2 Planned Non-Emergency Deviations (Single Subject Exception)

A planned deviation involves circumstances in which the specific procedures called for in a protocol are not in the best interests of a specific patient. It is a deviation that is anticipated and receives prior approval by the PI and the IRB.

16.2 Reporting of Deviations

16.2.1 Reporting Unplanned Deviations

For any such deviation, the Study PI will notify the COH DSMC and IRB within 5 calendar days of its occurrence via iRIS in accordance with the Clinical Research Protocol Deviation policy.

A list of these deviations will be submitted along with the Protocol Management Team (PMT) reports to the COH DSMC.

16.2.2 Reporting Planned Non-Emergency Deviations/ Single Subject Exceptions

Any planned deviation must be submitted as a "planned protocol deviation" via iRIS in accordance with IRB guidelines and the Clinical Research Protocol Deviation policy. An IRB approved planned deviation does not need to be submitted as a deviation to the DSMC.

17.0 ETHICAL AND REGULATORY CONSIDERATIONS

17.1 Ethical Standard

This study will be conducted in conformance with the principles set forth in The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research (US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, April 18, 1979) and the Declaration of Helsinki.

17.2 Regulatory Compliance

This study is to be conducted in compliance with the IRB approved protocol and according to the following considerations:

- US Code of Federal Regulations (CFR) governing clinical study conduct
  - Title 21 Part 11 – Electronic Records; Electronic Signatures
  - Title 21 Part 50 – Protection of Human Subjects
  - Title 21 Part 54 – Financial Disclosure by Clinical Investigators
  - Title 21 Part 56 – Institutional Review Boards
  - Title 21 Part 58 – Good Laboratory Practice for Nonclinical Laboratory Studies
  - Title 21 Part 312 – Investigational New Drug Application
  - Title 45 Part 46 – Protection of Human Subjects
- US Federal legislation, including but not limited to
  - Health Insurance Portability and Accountability Act of 1996
  - Section 801 of the Food and Drug Administration Amendments Act

- Applicable state and local laws. For research occurring in California, this includes but is not limited to State of California Health and Safety Code, Title 17
- Applicable institutional research policies and procedures

17.3 Institutional Review Board

An Institutional Review Board (IRB) that complies with the federal regulations at 45 CFR 46 and 21 CFR 50, 56 and State of California Health and Safety code, Title 17, must review and approve this protocol, informed consent form and any additional documents that the IRB may need to fulfill its responsibilities (Investigator's Brochure, information concerning patient recruitment, payment or compensation procedures, or other pertinent information) prior to initiation of the study. Revisions to approved documents will require review and approval by the IRB before the changes are implemented in the study. All institutional, NCI, Federal, and State of California regulations must be fulfilled.

The IRB's written unconditional approval of the study protocol and the informed consent document must be in the possession of the investigator before the study is initiated.

The IRB will be informed of serious unexpected, unanticipated adverse experiences, and unanticipated problems occurring during the study, and any additional adverse experiences in accordance with the standard operating procedures and policies of the IRB; new information that may affect adversely the safety of the patients of the conduct of the study; an annual update and/or request for re-approval; and when the study has been completed.

17.4 Informed Consent

The Principal Investigator or IRB approved named designee will explain the nature, duration, purpose of the study, potential risks, alternatives and potential benefits, and all other information contained in the informed consent document. In addition, they will review the experimental subject's bill of rights if applicable, and the HIPAA research authorization form. Prospective participants will be informed that they may withdraw from the study at any time and for any reason without prejudice, including as applicable, their current or future care or employment at City of Hope or any relationship they have with City of Hope. Prospective participants will be afforded sufficient time to consider whether or not to participate in the research.

After the study has been fully explained, written informed consent will be obtained from either the prospective participant or his/her guardian or legal representative before study participation. The method of obtaining and documenting the informed consent and the contents of the consent must comply with the ICH-GCP and all applicable regulatory requirements.

A copy of the signed informed consent will be given to the participant or his/her legally authorized representative. The original signed consent must be maintained by the investigator and available for inspection by sponsor designated representatives, or regulatory authority at any time.

Informed consent is a process that is initiated prior to the individual agreeing to participate in the study and continues throughout study participation.

17.5 Participant Withdrawal

Participants may withdraw from the study at any time and for any reason without prejudice. The withdrawal must be documented per institutional policies.

Participant withdrawal may consist of any of the following with regard to study procedures and data collection:

- Withdrawal from study treatment, but agreement to continue with active study procedures and chart review and follow-up procedures.
- Withdrawal from study treatment and all active procedures, but agreement for chart review and follow-up procedures.
- Withdrawal from study treatment, all active procedures, and any future data collection.

Participants who agreed to the collection of research blood samples may withdraw consent to use their specimens, if they are not yet processed as detailed in the consent form. Once the PI and site PI is notified of this withdrawal of informed consent, the research specimens will not be used in any research. At that time, any of the existing specimens will be destroyed.

17.6 Special and Vulnerable Populations

17.6.1 Inclusion of Women and Minorities

The study is open anyone regardless of gender or ethnicity. If differences in outcome that correlate to gender, racial, or ethnic identity are noted, accrual may be expanded or additional studies may be performed to investigate those differences more fully.

Pregnant women are excluded from the study. Animal reproduction studies have not been conducted, and there are no controlled data in human pregnancy.

Therefore, vorinostat and pembrolizumab should not be taken by pregnant women.

17.6.2 Exclusion of Children

Children/ adolescents (< 18 years old of age) are excluded from this study because the historical comparator trials were conducted in adults. Future studies may be planned to include children/ adolescents.

17.6.3 Inclusion of HIV Positive Individuals

Participants with a history of HIV are excluded due to concerns about inadvertent augmentation of infectious and/or inflammatory activity.

17.6.4 Vulnerable Populations

45 CFR §46.111 (a)(3) and 45 CFR §46, Subparts B-D identifies children, prisoners, pregnant women, mentally incapacitated persons, or economically or educationally disadvantaged persons as vulnerable populations.

Adults lacking capacity to consent are not excluded from participation. This study does not pose additional risks for adults lacking capacity than for the general population. In such instances, informed consent will be sought and documented from the prospective participant's legally authorized representative in agreement with institutional policies and COH IRB approval.

17.7 Participant Confidentiality

Participant confidentiality is strictly held in trust by the investigators, study staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples in addition to any study information relating to participants.

This research will be conducted in compliance with federal and state requirements relating to protected health information (PHI), including the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). HIPAA regulations require a signed participant authorization informing the participant of the nature of the PHI to be collected, who will have access to that information and why, who will use or disclose that information, ant the rights of a research participant to revoke their authorization for use of their PHI. In the event that a participant revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of participant authorization. For participants that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the participant is alive) at the end of their scheduled study period.

Release of research results should preserve the privacy of medical information and must be carried out in accordance with Department of Health and Human Services Standards for Privacy of Individually Identifiable Health Information, 45 CFR 164.508. When results of this study are reported in medical journals or at meetings, identification of those taking part will not be disclosed and no identifiers will be used.

Medical records of participants will be securely maintained in the strictest confidence, according to current legal requirements. Data will be entered, analyzed and stored in encrypted, password protected, secure computers that meet all HIPAA requirements. All data capture records, drug accountability records, study reports and communications will identify the patient by initials and the assigned patient number. Source documents provided to coordinating center for the purpose of auditing or monitoring will be de-identified and labeled with the study number, subject ID, and if applicable patient initials.

The investigator/institution will permit direct access to source data and documents by sponsor representatives, the FDA, and other applicable regulatory authorities. The access may consist of trial-related monitoring/ auditing, IRB reviews, and FDA/regulatory authority inspections. The participant's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

Participant specimens will be de-identified (coded) prior to submission to research laboratories. The specimens will be labeled with the study number, subject ID, institution and

timepoint of collection. The key to the code will be maintained in the COH clinical trials management system which is a secure environment.

17.8 Use of Unused (Leftover) Specimens Collected for this Trial

Unused samples in existence at study completion (i.e. completion of all research activities under this study) will be either: (a) discarded or (b) placed in a COH IRB approved biorepository with clinical information and potentially PHI attached.

With regard to which option will apply, each site IRB may choose to either: (a) leave the determination to the participant via a question in the informed consent document, which would communicated to the study registrar (DCC) at the time of participant registration, OR b) may choose to make a single determination on behalf of their respective participants, and communicate that determination to their respective participants via the informed consent.

17.9 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study Sponsor (City of Hope) prior to participation in this study. All City of Hope investigators will follow the City of Hope conflict of interest policy.

All study personnel are required to disclose financial interests in the company involved with this study, Merck.

17.10 Financial Obligations, Compensation, and Reimbursement of Participants

The investigational drugs, pembrolizumab and vorinostat, will be provided free of charge by Merck. Should pembrolizumab become commercially available during the course of study treatment, the research participant and/or the insurance carrier may be asked to pay for the costs of the drug.

Neither the research participant nor the insurance carrier will be responsible for the research procedures related to this study.

The standard of care drugs and procedures provided will be the responsibility of the research participant and/or the insurance carrier. The research participant will be responsible for all copayments, deductibles, and other costs of treatment and diagnostic procedures as set forth by the insurance carrier. The research participant and/or the insurance carrier will be billed for the costs of treatment and diagnostic procedures in the same way as if the research participant were not in a research study.

In the event of physical injury to a research participant, resulting from research procedures, appropriate medical treatment will be available at the City of Hope or at the non-COH site to the injured research participant, however, financial compensation will not be available. There are no plans for City of Hope to provide financial compensation in the event of physical injury to a participant.

The research participant will not receive reimbursement or payment for taking part in this study.

17.11 Publication/Data Sharing

Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by City of Hope for the purposes of performing the study, will be published or passed on to any third party without the written approval of the Study PI. Any investigator involved with this study is obligated to provide City of Hope with complete test results and all data derived from the study.

The preparation and submittal for publication of manuscripts containing the study results shall be in accordance with a process determined by mutual written agreement among City of Hope and Merck. The publication or presentation of any study results shall comply with all applicable privacy laws, including, but not limited to, the Health Insurance Portability and Accountability Act of 1996.

In accordance with the U.S. Public Law 110-85 (Food and Drug Administration Amendments Act of 2007 or FDAAA), Title VIII, Section 801, this trial will be registered onto ClinicalTrials.gov and results will be reported on ClinicalTrials.gov within 12 months of the estimated or actual completion date of the trial, whichever date is earlier.

APPENDIX A: ECOG PERFORMANCE STATUS

ECOG Performance Status Scale [140]	
Grade	**Descriptions**
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.

APPENDIX B: REGISTRATION COVERSHEET

COH IRB#: A Phase I Study of Pembrolizumab Plus Vorinostat for Relapsed or Refractory Diffuse Large B-cell Lymphoma, Follicular Lymphoma, and Hodgkin Lymphoma

Data Coordinating Center:
City of Hope
1500 Duarte Road
Duarte, CA 91010
Email: DCC@coh.org (use #secure# in subject line)

Site Principal Investigator
Name:
Address:

Phone:
Fax:
e-mail:

CRA/Study Coordinator:	Contact Number:
Patient's Initials: (F M L):	Institution:
Medical Record No:	Investigator/Treating Physician:
Patient's DOB:	IRB approval valid until (date):
Sex: _____Male _____Female	Date Informed Consent Signed:
	Projected start date of treatment:

Race		Ethnicity		Method of Payment:_____	
☐	Black	☐	Hispanic	Codes:	
☐	Caucasian	☐	Non-Hispanic	**01** Private	**06** Military or Veterans Adm. sponsored
☐	Asian	☐	Other_____	**02** Medicare	**07** Self-pay (no insurance)
☐	American Indian			**03** Medicare & private ins.	**08** No means of payment (no insurance)
☐	Native Hawaiian/Pacific Islander			**04** Medicaid	**09** Unknown
☐	Other_____ _____			**05** Medicaid & Medicare	

Reason for Screen Failure:

Reason for Failing to Initiate Protocol Therapy:

APPENDIX C: THE 2014 LUGANO CLASSIFICATION

The 2014 Lugano Classification will be used in this study for assessment of tumor response. PET/CT will be used study for HL and DLBCL, and is acceptable for FL, while CT with IV contrast (or MRI) can be used for FL.

Response	Site	CT-Based Response	PET-CT Based Response
Complete Response		Complete radiologic response (all of the following)	Complete metabolic response (even with a persistent mass)
	Lymph nodes and extralymphatic sites	• Target nodes/nodal masses must regress to ≤1.5 cm in longest diameter. • No extralymphatic sites of disease.	• Score ≤ 3* with or without a residual mass on 5-point scale†. • It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (e.g., with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake.
	Nonmeasured lesion	Absent	Not applicable
	Organ enlargement	Regress to normal	Not applicable
	New lesions	None	None
	Bone marrow	Normal by morphology; if determinate, IHC negative	No evidence of FDG-avid disease in marrow
Partial Response		Partial remission (all of the following)	Partial metabolic response
	Lymph nodes and extralymphatic sites	• ≥ 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites • When a lesion is too small to measure on CT, assign 5 mm X 5 mm as the default value • When no longer visible, 0 X 0 mm • For a node > 5 mm X 5 mm, but smaller than normal, use actual measurement for calculation	• Score 4 or 5† with reduced uptake compared with baseline and residual mass(es) of any size • At interim, these findings suggest responding disease • At end of treatment, these findings indicate residual disease

Response	Site	CT-Based Response	PET-CT Based Response
	Nonmeasured lesion	Absent/normal, regressed, but no increase	Not applicable
	Organ enlargement	Spleen must have regressed by > 50% in length beyond normal	Not applicable
	New lesions	None	None
	Bone marrow	Not applicable	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan
No response or stable disease		Stable disease	No metabolic response
	Target nodes/nodal masses, extranodal lesions	< 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met	Score 4 or 5† with no significant change in FDG uptake from baseline at interim or end of treatment
	Nonmeasured lesion	No increase consistent with progression	Not applicable
	Organ enlargement	No increase consistent with progression	Not applicable
	New lesions	None	None
	Bone marrow	Not applicable	No change from baseline
Progressive disease		Progressive disease requires at least 1 of the following	Progressive metabolic disease
	Individual target nodes/nodal masses	PPD progression:	Score 4 or 5 with an increase in intensity of uptake from baseline and/or
	Extranodal lesions	An individual node/lesion must be abnormal with: • Longest diameter (LDi) > 1.5 cm and • Increase by ≥ 50% from PPD nadir and • An increase in LDi or smallest diameter (SDi) from nadir • 0.5 cm for lesions ≤ 2 cm • 1.0 cm for lesions > 2 cm	• New FDG-avid foci consistent with lymphoma at interim OR • end-of-treatment assessment

Response	Site	CT-Based Response	PET-CT Based Response
		• In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (e.g., a 15-cm spleen must increase to 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline • New or recurrent splenomegaly	
	Nonmeasured lesion	New or clear progression of preexisting nonmeasured lesions	None
	New lesions	• Regrowth of previously resolved lesions • A new node > 1.5 cm in any axis • A new extranodal site < 1.0 cm in any axis; if > 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma • Assessable disease of any size unequivocally attributable to lymphoma	• New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). • If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered.
	Bone marrow	New or recurrent involvement	New or recurrent FDG-avid foci

Measured dominant lesions:

Up to six of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas.

Non-nodal lesions include those in solid organs (e.g., liver, spleen, kidneys, lungs), GI involvement, cutaneous lesions, or those noted on palpation.

Nonmeasured lesions:

Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites (e.g., GI tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response, but should be no higher than surrounding normal physiologic uptake (eg, with marrow activation as a result of chemotherapy or myeloid growth factors).

*A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid undertreatment).

†*PET 5-point score*:

1, no uptake above background; 2, uptake ≤ mediastinum; 3, uptake > mediastinum but ≤ liver; 4, uptake moderately > liver; 5, uptake markedly higher than liver and/or new lesions; X, new areas of uptake unlikely to be related to lymphoma.

Abbreviations:

CT, computed tomography; FDG, fluorodeoxyglucose; IHC, immunohistochemistry; LDi, longest transverse diameter of a lesion; MRI, magnetic resonance imaging; PET, positron emission tomography; PPD, cross product of the LDi and perpendicular diameter; SDi, shortest axis perpendicular to the LDi; SPD, sum of the product of the perpendicular diameters for multiple lesions.

APPENDIX D: TISSUE SHIPPING GUIDELINES TO CITY OF HOPE PATHOLOGY CORE

*These guidelines apply to **non-COH sites** only.*

All biological material must be shipped according to applicable government and International Air Transport Association (IATA) regulations.

Shipping guidelines can also be found on the FedEx website.

1. Aim to ship samples on a **Monday through Wednesday**. If this is not feasible, advance arrangements should be made with City of Hope Pathology Core (DL-PATHCORE-BiospecimenSupport@COH.org).

2. Notify City of Hope Pathology Core (DL-PATHCORE-BiospecimenSupport@COH.org) of impending shipment. To request a FedEx shipping label, email DCC@coh.org and indicate the planned shipment date.

3. **Slides/ Blocks:** Batch ship at room temperature via FedEx. During extreme heat, include refrigerated (not frozen) gel packs or gel insulators.

   It is recommended to ship samples via FedEx overnight (for a delivery by 3 pm or earlier the next day) or FedEx 2-day (with a morning delivery). During extreme heat, ship via FedEx overnight (for a delivery ideally by 10.30 am, or 3 pm the next day).

4. **Frozen samples** should be batch shipped on dry ice via FedEx overnight (for a delivery by 10.30 am the next day). The shipment should contain enough dry ice to last at least 72 hours.

5. On the day of shipment, email the sample shipment information to City of Hope Pathology Core (DL-PATHCORE-BiospecimenSupport@COH.org).

6. Ship samples with a **copy of the correlative tissue form (Appendix J)** and a **copy of the pathology report** to:

Karen Miller
COH Pathology Core
City of Hope National Medical Center
1500 E. Duarte Road
Familian Science (Building 084), Room 1207
Duarte, CA 91010
Telephone: 626-218-8408
Email: DL-PATHCORE-BiospecimenSupport@COH.org

APPENDIX E: TISSUE SHIPPING GUIDELINES TO THE JACKSON LABORATORY (FL PATIENTS ONLY)

PER COH PROTOCOL # 17072

*These guidelines apply to **COH** only, for the shipping of tissue from **FL patients** only.*

Follow the requirements for the proper packaging and shipping of biomedical material found in 42 CFR Part 72 - Interstate Shipment of Etiologic Agents Centers for Disease Control and Prevention, Office of Health and Safety Biosafety Branch.

Laboratory receiving samples:	Dr. Reddi's laboratory
When to ship:	Batch ship slides/ paraffin scrolls via overnight courier
Temperature conditions of shipment:	Room temperature
Days to ship:	**Monday-Wednesday** for receipt Tuesday-Friday by the laboratory. If this is not feasible, advance arrangements should be made with Dr. Honey Reddi or designee.

1. Request shipment billing details from the COH Study Coordinator.
2. **On the day of shipment**, notify via email the tracking number to:
    a. Dr. Honey Reddi or designee and
    b. the COH Data Coordinating Center (DCC@coh.org)
3. Ship samples to with the sample manifest:

Dr. Honey Reddi
Clinical Lab Director
10 Discovery Drive
The Jackson Laboratory for Genomic Medicine
Farmington, CT
Phone: 860.837.2062
Email: Honey.Reddi@jax.org

APPENDIX F: CORRELATIVE BLOOD COLLECTION FORM FOR NON-COH SITES ONLY

Subject ID (issued by DCC):	Participant Initials (F, M, L) (if applicable):
Institution:	

To be used by **non-COH sites** for the following blood samples being sent to **COH APCF**:

- Green-top tubes from **all** patients.
- BCT tubes from **HL and DLBCL patients only**.

Sample #	Timepoint of Collection *	Expected Volume	Tube Type Used (Select One)	Collected Volume	Time of Collection	Date of Collection	Indicate which sample was collected
1.	Cycle 1, Day 1	20 mL	Green-top	_____ mL	____:____ AM/ PM	____/____/____	☐
		20 mL	Cell-free DNA BCT	_____ mL	____:____ AM/ PM	____/____/____	☐
2.	Cycle 2, Day 1	20 mL	Green-top	_____ mL	____:____ AM/ PM	____/____/____	☐
		20 mL	Cell-free DNA BCT	_____ mL	____:____ AM/ PM	____/____/____	☐
3.	Cycle 5, Day 1	20 mL	Green-top	_____ mL	____:____ AM/ PM	____/____/____	☐
		20 mL	Cell-free DNA BCT	_____ mL	____:____ AM/ PM	____/____/____	☐
4.	Cycle 9, Day 1	20 mL	Cell-free DNA BCT	_____ mL	____:____ AM/ PM	____/____/____	☐
5.	Cycle 13, Day 1	20 mL	Cell-free DNA BCT	_____ mL	____:____ AM/ PM	____/____/____	☐
6.	Cycle 17, Day 1	20 mL	Cell-free DNA BCT	_____ mL	____:____ AM/ PM	____/____/____	☐
7.	Cycle 21, Day 1	20 mL	Cell-free DNA BCT	_____ mL	____:____ AM/ PM	____/____/____	☐
8.	Cycle 25, Day 1	20 mL	Cell-free DNA BCT	_____ mL	____:____ AM/ PM	____/____/____	☐
9.	Cycle 29, Day 1	20 mL	Cell-free DNA BCT	_____ mL	____:____ AM/ PM	____/____/____	☐
10.	At Discontinuation	20 mL	Cell-free DNA BCT	_____ mL	____:____ AM/ PM	____/____/____	☐

* Peripheral blood is collected prior to study treatment on Day 1 of each indicated cycle.

A copy of this form should accompany the sample shipments to COH APCF. **Refer to the blood shipping guidelines for shipping instructions to COH APCF (Appendix H).**

CRA/Study Coordinator/ Nurse:	Contact Number:
CRA/Study Coordinator/ Nurse Signature:	Date:

APPENDIX G: CORRELATIVE BLOOD COLLECTION FORM FOR ALL SITES (FOR FL PATIENTS ONLY)

Subject ID (issued by DCC):	Participant Initials (F, M, L) (if applicable):
Institution:	

To be used by **all sites** for the following blood samples being sent to the **Jackson Laboratory**:

- BCT tubes from **FL patients only**.

Sample #	Timepoint of Collection *	Expected Volume	Tube Type Used (Select One)	Collected Volume	Time of Collection	Date of Collection	Indicate which sample was collected
1.	Cycle 1, Day 1	20 mL	Cell-free DNA BCT	_____ mL	____:____ AM/ PM	____/____/____	☐
2.	Cycle 2, Day 1	20 mL	Cell-free DNA BCT	_____ mL	____:____ AM/ PM	____/____/____	☐
3.	Cycle 5, Day 1	20 mL	Cell-free DNA BCT	_____ mL	____:____ AM/ PM	____/____/____	☐
4.	Cycle 9, Day 1	20 mL	Cell-free DNA BCT	_____ mL	____:____ AM/ PM	____/____/____	☐
5.	Cycle 13, Day 1	20 mL	Cell-free DNA BCT	_____ mL	____:____ AM/ PM	____/____/____	☐
6.	Cycle 17, Day 1	20 mL	Cell-free DNA BCT	_____ mL	____:____ AM/ PM	____/____/____	☐
7.	Cycle 21, Day 1	20 mL	Cell-free DNA BCT	_____ mL	____:____ AM/ PM	____/____/____	☐
8.	Cycle 25, Day 1	20 mL	Cell-free DNA BCT	_____ mL	____:____ AM/ PM	____/____/____	☐
9.	Cycle 29, Day 1	20 mL	Cell-free DNA BCT	_____ mL	____:____ AM/ PM	____/____/____	☐
10.	At Discontinuation	20 mL	Cell-free DNA BCT	_____ mL	____:____ AM/ PM	____/____/____	☐

* Peripheral blood is collected prior to study treatment on Day 1 of each indicated cycle.

A copy of this form should accompany the sample shipments to Dr. Reddi's laboratory. Refer to Appendix I for **shipping instructions** to Dr. Reddi's laboratory.

CRA/Study Coordinator/ Nurse:	Contact Number:
CRA/Study Coordinator/ Nurse Signature:	Date:

APPENDIX H: BLOOD SHIPPING GUIDELINES TO CITY OF HOPE APCF

*These guidelines apply to **non-COH sites** only, for the shipping of **all green-top tubes** and cell-free DNA BCT® (Streck) tubes from **HL and DLBCL (and not FL)** patients.*

Follow the requirements for the proper packaging and shipping of biomedical material found in 42 CFR Part 72 - Interstate Shipment of Etiologic Agents Centers for Disease Control and Prevention, Office of Health and Safety Biosafety Branch.

1. Aim to ship samples on a **Monday through Wednesday**. If this is not feasible, advance arrangements should be made with Leslie Smith-Powell (LSmith-Powell@coh.org) or Stephanie Lee (stlee@coh.org) or their representative.

1. Blood samples in **green-top tubes** will be sent **overnight at around +4°C** with a refrigerated cool pack in an appropriate container via FedEx. Cell-free BCT tubes will be shipped together with green tubes for the first 3 time points. Starting from C9, cell-free BCT tubes should be shipped as as soon as possible but no more than 3 days after being drawn via overnight courier at ambient temperature.

2. **On the day of shipment**, email Leslie Smith-Powell (LSmith-Powell@coh.org) or Stephanie Lee (stlee@coh.org) or their representative the FedEx shipment #.

3. Ship samples with a **copy of the correlative blood collection form** and a **copy of the latest CBC results (with differential)** and the **date of the test** to:

Dr. Tim Synold
Analytical Pharmacology Core Facility
Shapiro 1042
City of Hope National Medical Center
1500 E. Duarte Road
Duarte, CA 91010

APPENDIX I: BLOOD SHIPPING GUIDELINES TO THE JACKSON LABORATORY (FL PATIENTS ONLY)

PER COH PROTOCOL # 17072

*These guidelines apply to **all sites**, for the shipping of **cell-free DNA BCT® (Streck) tubes** from **FL patients only**.*

Follow the requirements for the proper packaging and shipping of biomedical material found in 42 CFR Part 72 - Interstate Shipment of Etiologic Agents Centers for Disease Control and Prevention, Office of Health and Safety Biosafety Branch.

Laboratory receiving samples:	Dr. Reddi's laboratory
When to ship:	As soon as possible but no more than 3 days after being drawn, should be shipped via overnight courier
Temperature conditions of shipment:	Ambient temperature
Days to ship:	**Monday-Wednesday** for receipt Tuesday-Friday by the laboratory. If this is not feasible, advance arrangements should be made with Dr. Honey Reddi or designee.

1. Request shipment billing details from the COH Study Coordinator.
2. **On the day of shipment**, notify via email the tracking number and a copy of Blood Collection Form to:
    a. Dr. Honey Reddi or designee and
    b. The COH Data Coordinating Center (DCC@coh.org)
3. Ship samples with a copy of the **Blood Collection Form** to:

Dr. Honey Reddi
Clinical Lab Director
10 Discovery Drive
The Jackson Laboratory for Genomic Medicine
Farmington, CT
Phone: 860.837.2062
Email: Honey.Reddi@jax.org

APPENDIX J: CORRELATIVE TISSUE FORM FOR SHIPPING TO COH PATHOLOGY CORE

A copy of this form should accompany the sample shipments to COH Pathology Core.
Non-COH sites: refer to Appendix D for shipping instructions to COH Pathology Core.

COH IRB number: 17080	Shipping date (MM-DD-YYYY): _____/_____/_____
Subject ID (issued by DCC):	Participant Initials (F, M, L) (if applicable):
Institution:	
Date of collection/ biopsy (MM-DD-YYYY): _____/_____/_____	
Time point: ☐ Baseline ☐ Progression	
Diagnosis:	
Tissue type (FFPE scrolls, slides, biopsies):	
Number of scrolls:	Number of slides:

CRA/Study Coordinator/Nurse Printed Name:
CRA/Study Coordinator/Nurse Signature:
Contact Number:

APPENDIX K: EXPEDITED REPORTING COVERSHEET

NOTIFICATION OF UNANTICIPATED PROBLEM/SERIOUS ADVERSE EVENT

For Use by Participating Institutions Only

THIS FORM ALONG WITH A COPY OF THE MEDWATCH 3500 OR IRB REPORTING FORM MUST BE **EMAILED** TO DCC@COH.ORG WITHIN 24 HOURS OF KNOWLEDGE OF ONSET OF SERIOUS ADVERSE EVENT OR UNANCTICIPATED PROBLEM

COH IRB #_____- Participating Site IRB # _____

From:	Date:
Phone No.:	Email:
Reporting Investigator:	
Event:	
Participant ID:	Institution:
Date Event Met Reporting Criteria (as defined in protocol):	

Type of Report:	☐ Initial ☐ Follow-up
CTCAE Grade:	☐ G1/mild ☐ G2/moderate ☐ G3/severe ☐ G4/life threatening ☐ G5
Attribution to **pembrolizumab:**	☐ Unrelated ☐ Unlikely ☐ Possible ☐ Probable ☐ Definite
Attribution to **vorinostat**:	☐ Unrelated ☐ Unlikely ☐ Possible ☐ Probable ☐ Definite
Historical/Known Correlation to **pembrolizumab**:	☐ Expected ☐ Unexpected
Historical/Known Correlation to **vorinostat**:	☐ Expected ☐ Unexpected
Meets Definition of Serious AE:	☐ Serious ☐ Non-serious
Meets Definition of Unanticipated Problem:	☐ UP ☐ Not a UP
Has the event been reported to the following institution's IRB?	☐ No ☐ Yes; Date:_____/____/_____

Authorized Investigator Signature:	Date:____/____/____

APPENDIX L: LYRIC CRITERIA

Lugano Classification was developed based on treatment with cytotoxic agents [122]. Immunotherapeutic drugs, may produce antitumor effects by potentiating endogenous cancer-specific immune responses. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents, and can manifest as clinical responses after initial increases in tumor burden or even the appearance of new lesions. Thus, the 2014 Lugano Classification may not provide an accurate assessment of response to immunotherapeutic agents. Provisional modification of the Lugano criteria (LYRIC Criteria) may be used to assess participants who meet progressive disease per Lugano Classification [28, 122].

Complete Response	Partial Response	Progressive Disease
Same as Lugano	Same as Lugano	As with Lugano with the following **exceptions**: **Indeterminate response (IR)** • IR1: ≥50% increase in SPD of up to 6 measurable lesions in first 12 weeks of therapy without clinical deterioration • IR2: <50% increase in the overall SPD with *a.* Appearance of a new lesion(s), or *b.* ≥50% increase in PPD of a lesion or set of lesions at any time during treatment • IR(3): Increase in FDG uptake without a concomitant increase in lesion size or number • Patients with IR should continue on therapyand have repeat imaging after an additional 12 weeks (or sooner if clinically indicated). Progressive disease criteria in these patients will be met if: • IR1: An additional increase in the target SPD of ≥ 10% between the first IR1 timepoint and the SPD being assessed; or an increase in ≥ 5mm in either dimension of at least one lesion for lesions ≤ 2cm and 10mm for lesions > 2cm. • IR2: the new or growing lesion(s) should be added to the target lesions (total of no more than 6) and there is PD if the SPD if the newly defined set of target lesions has increased ≥50% from their nadir value (which may precede the IR time point). • IR3: There is evidence of PD by an increase in lesion size or the development of new lesions.
Abbreviations: SPD, sum of the product of the diameters; PPD, product of the perpendicular diameters.		

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