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TITLE: A single arm Phase I/II study of MK-3475 combined with vorinostat for recurrent unresectable and/or metastatic squamous cell head and neck cancer and recurrent unresectable and/or metastatic salivary gland malignancies

IND NUMBER: IND exempt

Fred Hutchinson Cancer Research Center Protocol ID: 9383

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1.0 TRIAL SUMMARY

Abbreviated Title	MK-3475 and vorinostat in head and neck cancer
Trial Phase	Phase I/II
Clinical Indication	Recurrent/Metastatic squamous cell head and neck carcinoma and salivary gland cancer
Trial Type	Open label single arm study
Type of control	None
Route of administration	IV (MK-3475) and oral (Vorinostat)
Trial Blinding	None
Treatment Groups	Single Arm Combination study
Number of trial subjects	Cohort 1 (squamous cell carcinoma) =35 Cohort 2 (salivary gland cancer) =35
Estimated duration of trial	24 months
Duration of Participation	24 months maximum for each patient

1.1 INDICATION

COHORT 1 Recurrent unresectable and/or metastatic squamous cell carcinomas of the head and neck (RMHNSCC)

COHORT 2 Recurrent unresectable and/or metastatic salivary gland carcinomas (RMSGC)

2.0 TRIAL DESIGN

2.1 Trial Design

This study is an open label, single arm study which will enroll in patients with RMHNSCC and RMSGC. Positive tumor PDL1 expression by IHC will not be required for enrollment.

All patients with receive MK-3475 and vorinostat in combination. Vorinostat will be started on the same day as the initiation of MK-475 200 mg flat dose given Q21 days and continued through the 21 day cycle. Vorinostat will be given 5 out of 7 days at a dose of 400mg QD.

Vorinostat and MK-3475 have well defined toxicities as single agents and have non-overlapping mechanisms of action. The safety of the two agents used in combination has not been previously described; therefore the study will be conducted in a phase I/II design.

2.1.1 Phase I run in

Both drugs are FDA approved for other disease indications, with safety and tolerability well described at the approved doses. Therefore the limited phase I portion of this study aims to

assess the safety and tolerability of this drug combination at their established doses. There will be no dose escalation cohorts within this phase I run in group.

The first six patients will constitute the phase I portion of this study. These initial 6 patients may come from either cohort and will be assessed for dose limiting toxicities (DLTs, defined in Section 2.1.1.1) after completion of cycle #1. After these first 6 patients initiate cycle #1, enrollment to the study will be temporarily halted, and a formal DLT evaluation of all 6 patients will be conducted.

If ≤ 2 of these six patients experience DLTs after completion of cycle #1, then the study will proceed to the phase II portion, using MK-3475 200mg IV Q21 days and Vorinostat 400mg PO 5 out of 7 days (x 3 weeks) of each 21 day cycle.

If > 2 of these first 6 patients experience a DLT upon completion of cycle #1, the study will proceed to the phase II portion using MK-3475 IV 200mg Q28 days Vorinostat 300mg daily 5 out of 7 days (x 4 weeks) of each 28 day cycle.

Only upon completion of the DLT evaluation for these first 6 patients and the determination of appropriate Phase II dose, will enrollment reopen for the phase II expansion.

2.1.1.1 Definition of Dose-Limiting Toxicities

All toxicities will be graded using National Cancer Institute (NCI) CTCAE Version 4.0 (see Appendix).

The occurrence of any of the following toxicities during Cycle 1 will be considered a DLT, if judged by the Investigator to be possibly, probably or definitely related to study drug administration:

1. Grade 4 non-hematologic toxicity (not laboratory)

2. Grade 3 non-hematologic toxicity (not laboratory) lasting >3 days despite optimal supportive care.

3. Any Grade 3 or Grade 4 non-hematologic laboratory value if:
   - Medical intervention is required to treat the patient, or
   - The abnormality leads to hospitalization

4. Grade 3 or Grade 4 febrile neutropenia:
   - Grade 3 is defined as ANC <1000/mm3 with a single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of ≥38 degrees C (100.4 degrees F) for more than one hour
   - Grade 4 is defined as ANC <1000/mm3 with a single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of ≥38 degrees C (100.4

degrees F) for more than one hour, with life-threatening consequences and urgent intervention indicated.

5. Prolonged delay (>2 weeks) in initiating cycle 2 due to treatment-related toxicity

6. Hematologic toxicity requiring dose modifications as outlined in Section 5.1.2.4

7. Grade 5 toxicity.

2.1.2. Phase II expansion

After the first 6 patients have been assessed for DLTs upon completion of cycle 1 of treatment, and the appropriate vorinostat dose and MK-3475 dosing interval determined for phase II expansion, additional patients will be enrolled with RMHNSCC (Cohort 1) and RMSCG (Cohort 2) to total 35 patients in each cohort. Patients enrolled in the phase I and II portioins will be used to assess the safety and efficacy outcomes of interest in each cohort.

Patients will be evaluated every 9 weeks (63 ± 7 days) with radiographic imaging to assess response to treatment. All imaging will be assessed using Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 Patients will also be assessed by immune response criteria (IrRC – Appendix) for determination of overall response rate (ORR) and progression-free survival (PFS). Adverse events will be monitored throughout the trial and graded in severity according to the guidelines outlined in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

Treatment with MK-3475 and vorinostat will continue until two years of therapy have been administered, or until

1. Documented disease progression (investigators may elect to continue MK-3475 treatment beyond progression in specific circumstances, unacceptable adverse event(s)
2. Intercurrent illness that prevents further administration of treatment
3. Investigator's decision to withdraw the subject
4. Subject withdraws consent,
5. Pregnancy of the subject,
6. Non-compliance with trial treatment or procedure requirements, or administrative reasons.

MK-3475 and vorinostat treated subjects who attain an investigator-determined confirmed complete response (CR) per RECIST 1.1 and IrRC may consider stopping trial treatment. Patients with a CR may continue on therapy for up to 2 cycles until a confirmatory scan is undertaken. If patients upon a confirmed CR progress they may continue therapy on a second course of therapy the combination until toxicity, progression. These subjects will be eligible for re-treatment for up to one year with MK-3475 and vorinostat after they have experienced radiographic disease progression at the discretion of the investigator according to the criteria in Section 5.1.4; this re-treatment will be the Second Course Phase. Response or progression in the Second Course Phase will not count towards the ORR and PFS of the primary endpoint in this trial.

After the end of treatment, each patient will be followed for a minimum of 30 days for adverse event monitoring (serious adverse events will be collected for up to 90 days after the end of treatment). Subjects will have post-treatment follow-up for disease status until death, withdrawing consent, or becoming lost to follow-up.

Participation in this trial will be dependent upon supplying tumor tissue from either a newly obtained formalin-fixed specimen, or an older formalin-fixed, paraffin-embedded specimen from locations not radiated prior to biopsy. Newly obtained formalin-fixed specimens are strongly encouraged unless clinically contraindicated as deemed by the treating physician. If new scientific data emerge that indicate that an existing biopsy or surgical specimen is suboptimal for identification of patients, only new biopsies will be acceptable for determination of PD-L1 status. The specimen will be evaluated at a central laboratory facility for expression status of PD-L1 in a prospective manner.

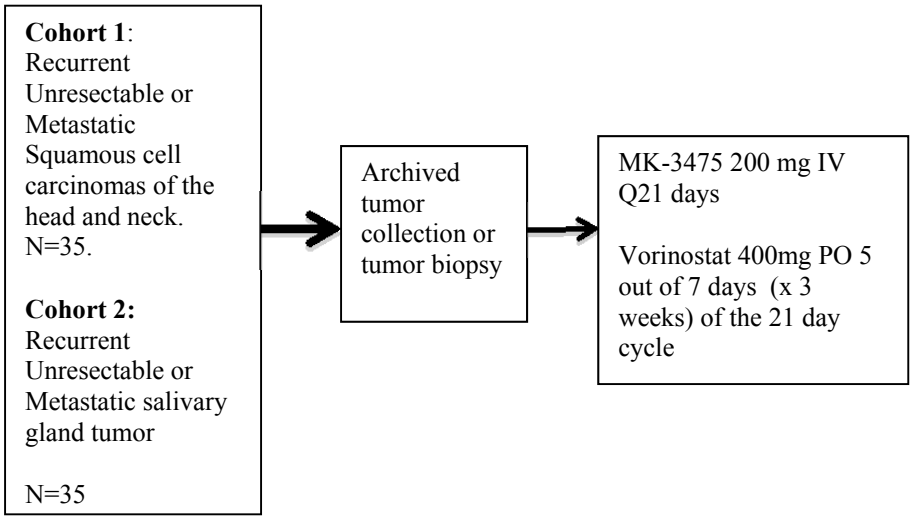
2.1.2.1 Safety assessments during the Phase II expansion

This investigator initiated study will be under the oversight of the Fred Hutchinson/University of Washington Cancer Consortium IRB and Data and Safety Monitoring committee. The investigators are ultimately responsible for monitoring the safety of patients who have entered this study and for alerting the Consortium IRB to any event that seems unusual in accordance with IRB policy. The investigator is responsible for the appropriate medical care of patients during the study. The investigator remains responsible to follow, through an appropriate health care option, adverse events that are serious or that caused the patient to discontinue before completing the study. The patient should be followed until the event resolves or stabilizes. Frequency of follow-up is left to the discretion of the investigator.

Safety measurements that will be used in the study include physical examinations and clinical laboratory tests (hematology and blood chemistries). The adverse event will be graded for toxicity using the NCI CTC version 4.0. Toxicity assessment will occur at the start of each cycle, or more frequently if clinically indicated. Any adverse events leading to a treatment interruption or dose reduction along with all adverse events that are grade 3 and higher will be recorded in the CRF. Adverse Events that meet Merck's definition of Event of Clinical Interest (refer to the Pembrolizumab ECI guidance document) will also be recorded.

The criteria for dose de-escalation for adverse events are outlined in Section 5.2. Any patient who requires two dose modifications or de-escalations will be taken off study.

2.2 Trial Diagram



3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

3.1 Primary Objective(s) & Hypothesis(es)

Objective: Determine the safety and tolerability of MK-3475 in combination with vorinostat patients with RMHNSCC and RMSGC

Hypothesis: The combination of MK-3475 and vorinostat is safe and well tolerated in patients with RMHNSCC and RMSGC

3.2 Secondary Objective(s) & Hypothesis(es)

1. **Objective**: Determine the objective response rates and disease control rates of the combination of MK-3475 and vorinostat in patients with RMHNSCC and RMSGC

   Hypothesis: The MK-3475 and vorinostat combination has clinical activity in RMHNSCC and RMSGC

2. **Objective:** Examine PD-L1 expression and T cell phenotype in archived tumor, on-treatment tumor biopsies, pre- and post-treatment blood samples and correlate these with clinical response to the drug combination.

   Hypothesis: RMHNSCC and RMSGC express PD-L1. PD-L1 expression, tumor and serum T cell phenotype correlate with response to combination of MK-3475 and vorinostat.

3. **Objective:** Determine median overall survival and progression free survival in and RMHNSCC and RMSGC patients enrolled in the study

Hypothesis: Patients receiving MK-3475 and vorinostat will have statistically significant overall survival and progression free survival among patients with RMHNSCC and RMSGC.

3.3 Exploratory Objective(s) and Hypothesis(es)

1. **Objective:** Explore peripheral T cell phenotype at baseline and after 3 cycles Vorinostat and MK-3475.

   Hypothesis: T cell phenotype is altered after exposure to Vorinostat and MK-3475, and will correlate with treatment response.

2. **Objective**: Measure expression of the proteins in the PD-1 family on baseline tumor samples and on treatment biopsies.

   Hypothesis: There is a relationship between response to MK-3475 and vorinostat and PD-1 protein family expression in both pre- and post-treatment tumor samples. Vorinostat given concurrently with MK-3475 will upregulate the expression of the PD-1 family of proteins.

If part 2 is added the same objectives will apply.

4.0 BACKGROUND & RATIONALE

4.1 Background

4.1.1 Recurrent Metastatic Squamous Cell Carcinomas

Annually approximately 60,000 new diagnoses of squamous cell carcinomas of the head and neck are diagnosed in the United States.[1] Tobacco and alcohol use are well recognized risk factors for the development of the disease, and marked socioeconomic disparity in the population at risk is well recognized. Over the last decade, there has been an epidemiologic shift in this population, with the emergence of high risk HPV related oropharynx squamous cell carcinoma.[2] This subset is unique in its molecular, pathologic and demographic features.

The majority of patients presenting with squamous cell carcinomas of the head and neck are diagnosed with locally advanced disease, with systemic metastasis being a late event. Although curative intent multimodality therapy is successful in a proportion of patients, most treatment failures are systemic.[3]

Patients with systemic metastases, or have locoregional disease recurrence that is not amenable to local therapy such as salvage surgery or radiation, have a poor prognosis, and a median survival of 6-9 months. Over the past 3 decades, multiple clinical trials have failed to demonstrate a survival advantage of combination chemotherapy to single agent therapy alone.[4-6] More recently the phase III EXTREME study, revealed a survival advantage to the administration of a platinum, 5-FU and cetuximab triplet compared to the platinum and 5-FU doublet.[7] Despite this, the regimen was associated with Grade 3 and higher toxicity in 80%

of patients enrolled, making it a difficult regimen to tolerate in this patient population with already significant comorbidity.

There is an urgent need to identify active, well tolerated agents in RMSCC. Immune checkpoint inhibition is a promising avenue in novel therapeutics in this disease, with a significant proportion of these malignancies expressing PD-L1 and robust populations of tumor infiltrating lymphocytes. Preliminary reports of activity of MK-3475 in this disease has led to expansion of head and neck squamous cell carcinomas in ongoing studies.[8]

4.1.2. Salivary Gland Malignancies

Salivary gland carcinomas represent <5% of all head and neck malignancies and are characterized by marked morphologic and biologic diversity. These arise from the secretory acini and associated myoepithelial cells in the three paired major salivary glands, and minor salivary glands located throughout the upper aerodigestive epithelium. The current WHO histological classification identifies 24 subtypes, with the most common being adenoid cystic carcinoma, mucoepidermoid carcinoma, salivary duct carcinomas and adenocarcinomas.[9] The current standard of care for early or locally advanced disease is curative intent resection followed by adjuvant radiation for tumors at high risk for recurrence. [10]

Currently, there is no standard of care for the treatment of incurable (unresectable and metastatic) salivary gland malignancies. Clinical trials that have examined the activity of systemic therapy have been difficult to interpret due to small numbers, heterogeneous patient populations, and the frequent observation of prolonged stable disease, a likely reflection of the indolent biology of certain salivary gland tumors, such as adenoid cystic carcinomas. Historical regimens tested more than 20 years ago have employed cisplatin and cisplatin-based combinations (response rates of 20% or lower).[11] Two of the largest contemporary studies conducted in North America have examined single agent paclitaxel (response rate 26% in non-adenoid cystic carcinoma subtypes, 0 in adenoid cystic carcinomas), and a gemcitabine carboplatin combination (response rate 24%).[12, 13] In these two studies median progression free survival was 5-6 months and median overall survival was 12-14 months, (KM estimates of 1 year overall survival 50%, 3 year overall survival 25%.) Even lower response rates have been demonstrated with prospective evaluation of the activity of various molecular targeted agents such as trastuzumab, gefitinib, imatinib and lapatinib, with essentially no objective response rates noted.[14-17]

Immunotherapy and anti-PD-1 targeted approaches are unexplored in this disease. Despite the disease's infrequency, this population is overrepresented in our tertiary clinical practice. Another advantage to studying this disease is the often abundant archived tissue (most patients undergo upfront curative intent resection) and the relative ease of obtaining additional tissue from accessible anatomical locations (upper aerodigestive tract and cervical lymph nodes).

Vorinostat is a histone deacetylase inhibitor that has been studied in adenoid cystic carcinomas. [18] There is preclinical data suggesting that HDAC inhibitors alter the biology of regulatory T cells and may increase tumor PD-L1 expression.[19-21]There is provocative

clinical data in NSCLC which suggests that epigenetic therapy may have synergistic activity with anti-PD-1 therapy.[22]

The Investigator's Brochure (IB) for MK-3475 and the package insert for vorinostat provide comprehensive background information on the mechanism of action of the mAb and the non-clinical data, including PK, pharmacodynamics, safety profile and anti-tumor activity of these two agents.

This study proposes the combination of vorinostat and MK-3475, with the goal of assessing the safety and tolerability of the combination. The study design will incorporate research serum and tissue collection for biomarker studies. Safety data and objective response rates of this combination will be used to determine if further study of the combination will be pursued.

4.1.3 Pharmaceutical and Therapeutic Background

4.1.3.1 MK-3475

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades.[23] Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies.[24-28] 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.

MK-3475 (previously known as SCH 900475) is a potent and highly selective humanized monoclonal antibody (mAb) of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2.

4.1.3.2 Vorinostat

Histone deacetylases (HDAC) are enzymes that catalyze the removal of acetyl groups from the lysine residues of proteins, including histones and transcription factors. HDAC inhibitors can induce tumor cell growth arrest, differentiation, or apoptosis in vitro and inhibit tumor growth in animals. The transcription of genes is regulated at least in part by acetylation of nucleosomal histones. The core nucleosomal histones are the most widely studied of the proteins that become acetylated following inhibition of HDAC activity12. In some cancer cells, there is an overexpression of HDACs, or an aberrant recruitment of HDACs to oncogenic transcription factors causing hypoacetylation of core nucleosomal histones.

Hypoacetylation of histones is associated with a condensed chromatin structure and repression of gene transcription. Inhibition of HDAC activity allows for the accumulation of acetyl groups on the histone lysine residues resulting in an open chromatin structure and transcriptional activation.

Vorinostat is a potent inhibitor of HDAC activity and binds directly to the catalytic pocket of HDAC enzymes. Vorinostat, at low nanomolar concentrations, inhibits the enzymatic activity of HDAC1, HDAC2 and HDAC3 (Class I) and HDAC6 (Class II). Concentrations of vorinostat that cause the accumulation of acetylated histones also induces cell cycle arrest, differentiation or apoptosis of transformed cells. Vorinostat induces apoptosis in a wide variety of transformed cells in culture, including cutaneous T-cell lymphoma (CTCL) cell lines, circulating atypical T-cells derived from patients with CTCL, human lymphoma cell lines and murine erythroleukemia (MEL) cells. Vorinostat also inhibits proliferation of cultured transformed human cells derived from leukemias, non-small cell lung carcinomas, colon carcinomas, central nervous system tumors, melanomas, ovarian carcinomas,renal cell carcinomas, prostate and breast cancers. In cultured human transformed cell lines, vorinostat

has synergistic or additive activity in combination with other cancer therapies, including radiation, kinase inhibitors, cytotoxic agents and differentiating agents.

In 2006 vorinostat received approval for cutaneous T-Cell lymphoma. Vorinostat has been clinically tested in clinical trials in many different solid and liquid tumor histologies including ongoing head and neck cancer (NCT01267240 - Capecitabine and Vorinostat in Treating Patients With Recurrent and/or Metastatic Head and Neck Cancer,; NCT01064921- Ph I Vorinostat in the Treatment of Advanced Staged Oropharyngeal Squamous Cell Carcinoma, NCT00336063 - Vorinostat and Azacitidine in Treating Patients With Locally Recurrent or Metastatic Nasopharyngeal Cancer or Nasal Natural Killer T-Cell Lymphoma).

Please refer to the investigators brochure and package insert in the appendices for additional details on vorinostat.

4.1.4 Preclinical and Clinical Trial Data

Refer to the Investigator's Brochure for Preclinical and Clinical data regarding MK-3475 and the package insert for vorinostat.

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

For **Cohort 1** Advanced incurable RMHNSCC carries a poor prognosis. Immune checkpoint modulation using monoclonal antibodies are undergoing active exploration in this group of malignancies. Preliminary data reported in abstract form in 2014 revealed that 78% of RMSCC screened for an ongoing MK-3475 phase Ib study, expressed PD-L1.[8] There have been observations of disease responses in this cohort of 60 patients, many of whom have been heavily pretreated with prior systemic agents.

For **Cohort 2** Patients with RMSGC have limited therapeutic options. Immune checkpoint modulation using monoclonal antibodies are unexplored in this group of malignancies and represent a promising treatment strategy. Prior clinical trials exploring the activity of various systemic chemotherapy agents and targeted agents have produced consistently poor objective response rates.[11-17] One of the challenges in clinical trial design and interpretation among salivary gland malignancies is the innate heterogeneity in the biological behavior of the various subtypes. Appropriate patient selection to account for the inherent differences in tumor biology is critical in defining drug activity in this disease. Therefore this study will enroll the most common aggressive subtypes of salivary gland malignancies, and require RECIST 1.1 criteria progression prior to study entry.

An intriguing avenue in the study of immune checkpoint inhibitors relates to potentiating the anti-tumor effect of the immunotherapy agents through various mechanisms such as augmenting T cell tumor infiltration, releasing cancer cell antigen and improving cancer antigen presentation using various chemokines, cytotoxic agents and vaccines.

Histone deacetylase inhibitors are a unique subset of therapeutic agents that as single agents appear to have cytotoxic activity in select solid and hematologic malignancies.[17,29] There is increasing preclinical data suggesting that HDAC inhibitor exposure, promotes APC function and proliferation of intratumoral cytotoxic T cells. There is also preclinical data supporting a reversal of epigenetic silencing of critical genes responsible for augmenting innate and adaptive immunity, as well as increased tumoral PD-L1 expression after NSCLC tumor cell line exposure to HDAC inhibition.[19,20] Objective and prolonged disease responses have been reported in patients with nonsmall cell lung cancer receiving anti-PDL-1/antiPD-1 monoclonal antibodies.[22] Evidence suggests that epigenetic modification of tumors may also enhance tumor antigenicity.[21]

4.2.2 Rationale for Dose Selection/Regimen/Modification

An open-label Phase I trial (KEYNOTE-001) is being 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 pembrolizumab (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.

In KEYNOTE-001, several randomized cohort evaluations of melanoma subjects receiving pembrolizumab (MK-3475) at doses of 2 mg/kg versus 10 mg/kg Q3W have been completed, and dose intervals of Q3W versus Q2W have also been completed. The clinical efficacy and safety data demonstrate a lack of clinically important differences in efficacy response or safety profile at either dose or either interval.

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

The choice of the 200 mg Q3W as an appropriate dose for fixed dosing is based on simulations performed using a population PK model of pembrolizumab which revealed that the fixed dose of 200 mg every 3 weeks provides 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. KEYNOTE-012 initially studied subjects using the 10 mg/kg every three weeks. An expansion cohort of an additional 100 patients with HNSCC has enrolled using the fixed 200 mg every three week dosing. Safety and efficacy assessment of this cohort is ongoing.

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.

4.2.3 Rationale for Endpoints

Both vorinostat and MK-3475 appear to be well tolerated as a single agents and have FDA approved doses and indications. These two drugs have non-overlapping mechanisms of action. There has been no reported clinical experience with the combination of vorinostat and MK-3475. Therefore a phase I/II design, wherein a limited phase I run in cohort is initially enrolled, was felt to be most appropriate to study this combination, with safety and tolerability as the primary endpoint of interest.

4.2.3.1 Efficacy Endpoints

There is intriguing preclinical and clinical data suggesting that epigenetic priming through HDAC inhibition may induce expression of PD-1 expression in tumor infiltrating lymphocytes and augment the immunologic anti-tumor response to MK-3475. Therefore exploring objective response rates to the combination of MK-3475 and vorinostat will be secondary endpoints. Overall survival and progression free survival will be examined in the entire cohort enrolled. If encouraging response rates, and overall and progression free survival are observed in this cohort of patients, further study of the combination in this disease will be justified.

4.2.3.2 Biomarker Research

Archival tissue will be collected from all patients participating in the study. Every attempt will be made to obtain fresh tissue after treatment with 3 cycles of the MK-3475 and vorinostat combination regardless of response to treatment. These samples will be submitted to Merck for tissue based assays.

Research serum samples will be obtained at the following timepoints baseline, after 3 cycles MK-3475 and vorinostat and at treatment discontinuation or disease progression. We intend to perform flow cytometric evaluation of CD3, CD4, CD8, CD14, PD-1, PD-L1, PD-L2 on peripheral blood mononuclear cells.

5.0 METHODOLOGY

5.1 Entry Criteria for Treatment at Trial Entry

5.1.1 Diagnosis/Condition for Entry into the Trial

Phase I run in: biopsy proven RMHNSCC with the following primary sites: nasopharynx, paranasal sinus, nasal cavity, skin/cutaneous sites. Patients with unknown head and neck primary sites will be enrolled. Patients with recurrent or metastatic squamous cell carcinomas of the head and neck (regardless of primary site) who are either unwilling to receive or have contraindications (deemed by treating physician) to standard systemic chemotherapy will also be eligible. Patients with biopsy proven RMSGC be eligible as well.

Since our center will be participating in a separate MK-3475 clinical trial (Keynote-40), the above group of patient will be prioritized for the phase I run in portion, and avoid overlap with Keynote -40.

Phase II expansion: biopsy proven RMHNSCC of any primary site (including unknown primary) and RMSGC will be eligible.

5.1.2 Subject Inclusion Criteria

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

1. Have disease progression by RECIST 1.1 criteria as determined by treating physician per investigator judgment within 3 months prior to enrollment.
2. Have received any number lines of prior systemic therapy (including systemic therapy in the curative intent setting).
3. Be willing and able to provide written informed consent for the trial and comply with the study visit requirements
4. Be ≥ 18 years of age on day of signing informed consent.
5. Have measurable disease based on RECIST 1.1.
6. Have provided tissue from an archival tissue sample or newly obtained core or excisional biopsy of a tumor lesion.
7. Have a performance status of 0 or 1 on the ECOG Performance Scale.
8. Demonstrate adequate organ function as defined in
9. Table 1, all screening labs should be performed within 10 days of treatment initiation.

Table 1 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1,500 /mcL
Platelets	≥100,000 / mcL
Hemoglobin	≥9 g/dL or ≥5.6 mmol/L
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
AST (SGOT) and ALT (SGPT)	≤ 1.5 X ULN
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 per institutional standard.	

10. 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.

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

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

13. Patient is < 5 years free of another primary malignancy, except: a) if the other malignancy is basal cell carcinoma or cervical carcinoma in situ or b) if the other primary malignancy is not considered clinically significant and is requiring no active intervention

5.1.3 Subject Exclusion Criteria

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

1. Is currently participating in or has participated in a study of an investigational agent or using an investigational device within 4 weeks of the first dose of treatment.

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

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

4. 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.

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

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

7. Has an active automimmune disease requiring systemic treatment within the past 3 months or a documented history of clinically severe autoimmune disease, or a syndrome that requires systemic steroids or immunosuppressive agents. Subjects with vitiligo or resolved childhood asthma/atopy would be an exception to this rule. Subjects that require intermittent use of bronchodilators or local steroid injections would not be excluded from the study. Subjects with hypothyroidism stable on hormone replacement or Sjogren's syndrome will not be excluded from the study.

8. Has evidence of interstitial lung disease or active, non-infectious pneumonitis.

9. Has an active infection requiring systemic therapy.

10. 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.

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

12. 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.

13. Has received prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways). Patients who have previously received MK-3475 or participated in an MK-3475 clinical trial will be ineligible.

14. Has received prior therapy with vorinostat or other epigenetic agent.

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

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

17. Has received a live vaccine within 30 days prior to the first dose of trial treatment.

18. Requires total parenteral nutrition and is unable to swallow pills or unable to take a suspension through a gastrostomy tube.

5.1.4 Inclusion and Exclusion Criteria for Second Course Phase (Retreatment Period for Post-Complete Response Relapse ONLY)

Subjects may be eligible to receive MK-3475 in the Second Course Phase of this study if the study remains open and the subject meets the following conditions:

- Stopped initial treatment with MK-3475 after attaining an investigator-determined confirmed response according to RECIST1.1 response criteria

- Was treated for at least 24 weeks with MK-3475 before discontinuing therapy

- Received at least four treatments with MK-3475 beyond the date when the initial CR was declared

- Experienced an investigator-determined confirmed cutaneous or radiographic disease progression after stopping their initial treatment with MK-3475

- Did not receive any anti-cancer treatment since the last dose of MK-3475

- Have a performance status of 0 or 1 on the ECOG Performance Scale
- Demonstrate adequate organ function as detailed in Section 5.1.2
- Female subject of childbearing potential should have a negative urine or serum pregnancy test within 72 hours prior to receiving retreatment with study medication.
- Female subjects of childbearing potential should be willing to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of study medication (Reference Section 5.7.2). Subjects of child bearing potential are those who have not been surgically sterilized or have not been free from menses for > 2 year.
- Male subjects should agree to use an adequate method of contraception starting with the first dose of study therapy through 120 days after the last dose of study therapy.
- Does not have a history or current evidence of any condition, therapy, or laboratory abnormality that might interfere with the subject's participation for the full duration of the trial or is not in the best interest of the subject to participate, in the opinion of the treating investigator.

Subjects who restart treatment will be retreated using the same guidelines for the combination of MK-3475 and vorinostat.

Visit and response criteria requirements are outlined in Section 6.1 – Trial Flow Chart for the second course

Patients upon progression might have requested an experimental biopsy to investigate tumor immunology at the time of progression.

5. 2 Trial Treatments

The treatment to be used in this trial is outlined below in Table 2.1 This is for initial treatment of patients upon trial entry and similarly for retreatment of patients after progression on a CR.

Table 2.1 MK-3475 in combination with vorinostat

Drugs	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period	Use
1. Vorinostat	400mg	QD 5 out of 7 days per week for 3 weeks (21 days) starting the day of MK-3475 infusion	Oral or via PEG	Maximum of 2 years	Experimental

Drugs	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period	Use
2. MK-3475	200mg	Q21 days	IV infusion	Maximum of 2 years	Experimental
The MK-3475 dosing interval may be increased due to toxicity as described in Section 5.2.1.2.					

Patients will initiate vorinostat at 400mg daily on the same day as MK-3475 200 mg IV Q21 days infusion. Vorinostat should be taken within 30 minutes of a meal. Vorinostat will be continued 5 out of 7 days throughout each week of the 21 day cycle.

Radiographic imaging (RECIST 1.1 and IrRC) will be completed at a minimum of 9 weeks of starting the MK-3475 and vorinostat combination. Patients who have objective responses or stable disease will continue therapy. Patients who obtain clinical benefit from the combination will be allowed to continue therapy for a maximum of 2 years, or until progression or severe toxicity, whichever comes first.

Patients can be treated for a maximum of 2 cycles before a confirmatory scan for a CR is performed.

Patients who do not achieve a RECIST 1.1 criteria objective response at the first radiographic evaluation can continue the combination of vorinostat and MK-347 provided that they do not demonstrate clinical deterioration (defined by the following parameters and determined by the treating physician):

1. Absence of signs and symptoms of disease progression
2. No decline in ECOG performance status
3. Absence of rapid disease progression
4. Absence of progressive tumor at critical anatomical sites (e.g. cord compression) requiring urgent alternative medical intervention.

Patients who receive a confirmed CR on trial may consider discontinuation of treatment. Upon progression they can be retreated on a second course of therapy according to Table 2.1. patients who progress on the second course of therapy are off study.

5.2.1 Dose Selection/Modification

5.2.1.1 Dose Selection

The rationale for selection of dose of MK-3475 to be used in this trial is provided in Section 4.0 – Background and Rationale.

Since MK-3475 will be dosed as a flat dose there will be no requirement to calculate a dose/kg for each patient unless a dose reduction is needed.

The approved dose of vorinostat is 400mg QD for CTCL. However, published clinical experience in additional clinical trials has suggested that dosing at 400 mg 5 out of 7 days reduces toxicity and increases tolerability of the drug compared to daily 400 mg use. Consequently, we propose the 5 out 7 day schedule for this trial.

5.2.1.2 Dose Modifications for MK-3475 and Vorinostat

Toxicity will be graded using Common Terminology Criteria for Adverse Events (CTCAE version 4.0). The protocol will change to CTCAE version 5.0 if is published within the course of the trial.

Because it there may be overlap in the toxicities of both agents, and difficulty in attributing toxicity to either agent, patients experiencing any Grade 3 toxicity (except those outlined in Table 3.1 and Section 5.2.1.4) or any Grade 4 toxicity will have ***both MK-3475 and vorinostat held until improvement of the adverse event to Grade 1 or baseline***.

Toxicity that requires more than two dose reductions or modifications of vorinostat will lead to discontinuation of the patient from the treatment phase of the study. ***Patients are not permitted to continue on vorinostat or MK-3475 dosing alone.*** In addition, no dose re-escalations are allowed during the study period unless toxicities are resolved to grade 1. Justification will be recorded in the source documents

Before initiation of subsequent cycles, each patient will be evaluated for possible toxicities that may have occurred after the previous treatment. All Grade 3 or 4 toxicities (except those specified in Table 3.1 and Section 5.2.1.4) should resolve to Grade 1 or baseline before re-initiation of study treatment. Dose modification will be made based on the toxicity with the greatest severity.

Table 3.1: Dose modification guidelines for MK-3475

Toxicity	Grade	Hold Treatment (Y/N)	Timing for restarting treatment	Dose/Schedule for restarting treatment	Discontinue Subject (after consultation with Sponsor)
Hematological Toxicity	1, 2	No	N/A	N/A	N/A
	3* *Excluding Grade 3 neutropenia, anemia, and thrombocytopenia See Section 5.2.1.4)	Yes	Toxicity resolves to Grade 0-1 or baseline	May increase the dosing interval by 1 week	Toxicity does not resolve within 12 weeks of last infusion *Permanent discontinuation should be considered for any severe or life-threatening event*
	4	Yes	Toxicity resolves to Grade 0-1 or baseline	May increase the dosing interval by 1 week	
Non-hematological toxicity	1	No	N/A	N/A	N/A

Toxicity	Grade	Hold Treatment (Y/N)	Timing for restarting treatment	Dose/Schedule for restarting treatment	Discontinue Subject (after consultation with Sponsor)
Note: Exception to be treated similar to grade 1 toxicity • Grade 2 alopecia • Grade 2 fatigue For additional information regarding Adverse Events with a potential Immune-Etiology reference Section 5.6.1.1. and Appendix 12.8	2	Consider withholding for persistent symptoms	Toxicity resolves to Grade 0-1 or baseline	*Clinical AE resolves within 4 weeks*: Same dose and schedule (reference Section 5.6.1.2 for recommendations regarding pneumonitis) *Clinical AE does not resolve within 4 weeks:* May increase the dosing interval by 1 week for each occurrence	Toxicity does not resolve within 12 weeks of last infusion
	3, 4	Yes	Toxicity resolves to Grade 0-1 or baseline	May increase the dosing interval by 1 week for each occurrence	Toxicity does not resolve within 12 weeks of last infusion *Permanent discontinuation should be considered for any severe or life-threatening event*

In case toxicity does not resolve to Grade 0-1 within 12 weeks after last infusion, trial treatment should be discontinued. With investigator and Sponsor agreement, subjects with a laboratory adverse event still at Grade 2 after 12 weeks may continue treatment in the trial only if asymptomatic and controlled. For information on the management of adverse events, see Section 5.6.1.

Subjects who experience a recurrence of the same severe or life-threatening event at the same grade or greater with re-challenge of MK-3475 should be discontinued from trial treatment.

5.2.1.3. Dose Modifications for Vorinostat

Because there may be overlap between vorinostat and MK-3475 toxicities, patients experiencing any Grade 3 toxicity (except those outlined in Table 3.1 and Section 5.2.1.4) or any Grade 4 toxicity will have ***both MK-3475 and vorinostat held until improvement of the adverse event to Grade 1 or baseline.***

The following table describes vorinostat dose levels for patients receiving MK-3475 and vorinostat combination ***for the phase I portion of the study***, This table will also be used in the Phase II portion of the ***study if the Vorinostat dose is determined to be 400mg***.

Table 3.2 Dose Reduction Steps for Vorinostat-Specific Related Toxicities

Starting Dose	1st dose reduction	2nd dose reduction	3rd Dose Reduction
Vorinostat	Vorinostat	Vorinostat	Discontinue therapy
4 capsules – 400 mg OR 8mL of 50mg/ml suspension	3 capsules – 300 mg OR 6mL of 50mg/mL suspension	2 capsules – 200 mg OR 4mL of 50mg/mL suspension	
5 out of 7 days	5 out of 7 days	5 out of 7 days	

If the phase I lead in portion determines that the phase II vorinostat dose is 300mg daily the following table will be used for vorinostat dose modifications.

Starting Dose	1st dose reduction	2nd dose reduction	3rd Dose Reduction
Vorinostat	Vorinostat	Vorinostat	Discontinue therapy
3 capsules – 300 mg OR 6mL of 50mg/mL suspension	2 capsules – 200 mg OR 4mL of 50mg/mL suspension	1 capsules – 100 mg OR 2mL of 50mg/mL solution	
5 out of 7 days	5 out of 7 days	5 out of 7 days	

Any of the following will necessitate vorinostat dose modification:

1. Grade 4 non-hematologic toxicity (not laboratory)

2. Grade 3 non-hematologic toxicity (not laboratory) lasting >3 days despite optimal supportive care.

3. Any Grade 3 or Grade 4 non-hematologic laboratory value if:

   - Medical intervention is required to treat the patient, or
   - The abnormality leads to hospitalization

4. Grade 3 or Grade 4 febrile neutropenia:

   Grade 3 is defined as ANC <1000/mm3 with a single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of ≥38 degrees C (100.4 degrees F) for more than one hour

Grade 4 is defined as ANC <1000/mm3 with a single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of ≥38 degrees C (100.4 degrees F) for more than one hour, with life-threatening consequences and urgent intervention indicated.

5. Prolonged delay (>2 weeks) in initiating cycle 2 due to treatment-related toxicity

6. Hematologic or gastrointestinal toxicity that mandates dose modification according to Section 5.2.1.4

5.2.1.4 Dose modification and supportive care for specific toxicities related to Vorinostat & MK-3475

5.2.1.4.1 Hematologic Toxicity

1. Neutropenia

Grade 3 (ANC ≥0.5 – 1.0 x 10^9 /L) Continue MK-3475 and Vorinostat dosing and maintain dose level.

Grade 4 (ANC less than 0.5 x 10^9 /L) Hold MK-3475 and vorinostat until ANC recovery to 1.0 x 10^9 /L. Dose adjustment according to Table 3.2 and 3.3. is mandatory.

To follow Grade 4 neutropenia, ANC values should be obtained per institutional guidelines; re-dosing decision may be made on local laboratory values. Duplicate samples should be sent to the central laboratory, whenever possible.

2. Anemia

Grade 3 (hemoglobin ≥6.5 – 8.0 g/dl): Continue MK-3475 and Vorinostat dosing and maintain dose level..

Grade 4 (hemoglobin less than 6.5 g/dl)

Hold MK-3475 and vorinostat until hemoglobin recovery to ≧ 8.0 g/dl. Supportive care and transfusion support per institutional guidelines should be implemented. Dose adjustment according to Table 3.2 and 3.3. is mandatory..

To follow Grade 4 anemia, Hgb values should be obtained per institutional guidelines; re-dosing decision may be made on local laboratory values. Duplicate samples should be sent to the central laboratory, whenever possible.

3. **Thrombocytopenia**

Grade 3 (platelet value >25,000 – 50,000/µL. Continue MK-3475 and Vorinostat dosing and maintain dose level..

Grade 4 (platelet value 25,000 µL or less)

Hold both MK-3475 and vorinostat (for up to 2 weeks) until platelet recovery to >50,000/µL has been observed with or without platelet transfusion. Dose adjustment according to Table 3.2 and 3.3. is mandatory.

To follow Grade 4 thrombocytopenia, platelet values should be obtained per institutional guidelines; re-dosing decision may be made on local laboratory values. Duplicate samples should be sent to the central laboratory, whenever possible.

4. **Lymphopenia**

Dose interruption or study discontinuation is not required for lymphopenia of any grade.

5.2.1.4.2 Gastrointestinal Toxicity

1. **Diarrhea**

Grade 3 or Grade 4 diarrhea: Hold MK-3475 and Vorinostat until resolution to Grade 1 or less, or to baseline. Dose modification for the two drugs will be followed as outlined by Tables 3.1 and 3.2

Some patients will experience diarrhea following vorinostat or the combination, mild-to-moderate in severity. To date, observation of diarrhea has tended to increase in frequency with continued dosing; both site personnel and patients should be told of the possibility of increased diarrhea with continued cycles.

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

Diarrhea should be managed aggressively, as Grade 2 Diarrhea may progress to Grade 3, necessitating interruptions in therapy. Consideration regarding use of prophylactic and/or supportive care should be made upon the first observation of

Grade 1 or higher Diarrhea. Non-prescription methods to improve diarrhea include: diet modification (increased fiber, certain brands of yogurt, such as Probiotics), and hydration. Anti-diarrheal prescriptions medications include: loperamide and diphenoxylate with atropine. Consider giving the patient a prescription for an antidiarrheals to be filled if needed on the first day of therapy.

2. Enterocolitis

Subjects should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus). In symptomatic subjects, infectious etiologies should be ruled out, and if symptoms are persistent and/or severe, endoscopic evaluation should be considered.

In subjects with severe enterocolitis (Grade 3), MK-3475 will be permanently discontinued and treatment with systemic corticosteroids should be initiated at a dose of 1 to 2 mg/kg/day of prednisone or equivalent. When symptoms improve to Grade 1 or less, corticosteroid taper should be started and continued over at least 1 month.

In subjects with moderate enterocolitis (Grade 2), MK-3475 should be withheld and anti-diarrheal treatment should be started. If symptoms are persistent for more than one week, systemic corticosteroids should be initiated (e.g., 0.5 mg/kg/day of prednisone or equivalent). When symptoms improve to Grade 1 or less, corticosteroid taper should be started and continued over at least 1 month. Regarding guidelines for continuing treatment with MK-3475, see Section 5.2. Additional data regarding management of this immune related adverse event will be included in Appendix 12.8

3. Nausea/Vomiting/Dehydration

Grade 3 Nausea/Vomiting/Dehydration lasting >72 hours despite aggressive supportive care OR **Grade 4** Nausea/ Vomiting/Dehydration(lasting any duration) will result in stepwise dose reduction as outlined in Tables 3.1. and 3.2. Until resolution of the toxicity to Grade 1 or less or to baseline, MK-3475 and vorinostat are to be held.

Supportive care for Nausea/Vomiting: Some patients will experience nausea following vorinostat or the combination, generally mild-to-moderate in severity. With subsequent cycles, many patients note that the sensation of nausea becomes less. Once documented nausea and/or vomiting has been observed, the use of antiemetics per institutional guidelines is strongly encouraged. Non-prescription methods to improve nausea include: antacids, antiulcer drugs, ginger ale or ginger lozenges. Encourage each patient to drink at least 2 liters of fluid each day to avoid dehydration. Anti-emetic prescriptions medications include: prochlorperazine,

lorazepam, or any of the 5-HT3 reuptake inhibitors (granisetron; ondansetron; palonosetron; dolasetron; or tropisetron). Consider giving the patient a prescription for an anti-emetics to be filled if needed on the first day of therapy.

Dehydration should be managed with aggressive hydration (either intravenous or oral fluids). Patients should be strongly encouraged to maintain significant oral fluid intake.

5.2.1.5 Initiation of subsequent cycles of therapy:

- MK-3475 and vorinostat are to be started on the same day. If an increase in MK-3475 dosing interval is required according to Table 3.1, vorinostat will be taken 5 out of 7 days for every week of the MK-3475 dosing interval.

- A new course of treatment may begin on the scheduled Day 1 of a new cycle if all non-hematological toxicity from the previous cycle has recovered to ≤ Grade 1 or baseline, and/or hematologic recovery documented as outlined in section 5.2.1.4.

Initiation of subsequent cycles of therapy may be delayed for up to 12 weeks to allow recovery from all drug-related toxicity. Alternately, the Investigator may choose to administer supportive care (blood product transfusions) for retreatment criteria to be met. If the recovery criteria are not met after a 12-week delay, the patient will be discontinued from study treatment unless, in the opinion of the Investigator, the patient is experiencing a clinical benefit, in which case a decision regarding continuation of treatment will be made on an individual patient basis in consultation with the Merck medical monitor. Justification will be recorded in the source documents.

When initiating a subsequent cycle, a minimum interval of 21 days should be observed between MK-3475 administrations (with no minimum interval for vorinostat).

Continuation of study therapy during a cycle:

Within any cycle, the dose/schedule of either study drug may be adjusted as necessary.

5.2.2. Timing of Dose Administration

Vorinostat and MK-3475 dose will both be initiated on day 1 of each treatment cycle after all procedures/assessments have been completed as detailed on the Trial Flow Chart (Section 6.0). Trial treatment may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons.

All trial treatments will be administered on an outpatient basis.

Oral vorinostat (400 mg) administered is once daily by mouth with food or within 0-30 minutes after a meal (if possible) for days 1-5 of each week in a week (21 day) treatment cycle. For any patient experiencing Grade 1 or higher drug-related fatigue, the Investigator should advise the patient to administer vorinostat prior to bedtime (See Section 3.2.6.3). On the day that MK-3475 is administered patient should take vorinostat a minimum of 2 hours before the MK-3475 infusion.

For patients unable to swallow pills, vorinostat will be administered as a 50mg/mL suspension. This solution will be prepared by investigational pharmacy and administered via gastrostomy tube or nasogastric tube. Gastrostomy tubes will be flushed with 20 mL of water before and after the suspension is administered. The dosing and dose reductions will follow Table 3.2.

MK-3475 will be administered as a 30 minute IV infusion (treatment cycle intervals may be increased due to toxicity as described in Section 5.2.1.2). Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -/ +10 minutes is permitted (i.e., infusion time is 30 minutes: - /+10 min).

5.3 Trial Blinding/Masking

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

5.4 Randomization or Treatment Allocation

All patients enrolled in this study will receive the combination of MK-3475 and vorinostat.

5.5 Concomitant Medications/Vaccinations (allowed & prohibited)

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

Hematopoetic growth factors will not be permitted in patients enrolled on this study.

5.5.1 Acceptable Concomitant Medications

All treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care.

5.5.2 Prohibited Concomitant Medications

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

- Anti-cancer systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than MK-3475
- Radiation therapy
    - Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed after consultation with Sponsor.
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however intranasal influenza vaccines (e.g. Flu-Mist®) are live attenuated vaccines, and are not allowed..
- Glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.

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

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

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

5.6 Rescue Medications & Supportive Care

5.6.1 Supportive Care Guidelines Specific for MK-3475

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

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

- Immune-related adverse events: Please see Section 5.6.1.1 below and the separate Pembrolizumab ECI guidance document regarding diagnosis and management of adverse experiences of a potential immunologic etiology.

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

Table 5 below shows treatment guidelines for subjects who experience an infusion reaction associated with administration of MK-3475.

Table 5 Infusion Reaction Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for < =24 hrs	**Stop Infusion and monitor symptoms.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g. from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. **Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from**	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of MK-3475 with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic).

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
	further trial treatment administration.	
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **Subject is permanently discontinued from further trial treatment administration.**	No subsequent dosing
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration. For Further information, please refer to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE) at http://ctep.cancer.gov		

5.6.1.1 Supportive Care Guidelines for Events of Clinical Interest and Immune-related Adverse Events (irAEs)

Events of clinical interest of a potential immunologic etiology (irECIs) may be defined as an adverse event of unknown etiology, associated with drug exposure and is consistent with an immune phenomenon. irAEs may be predicted based on the nature of the MK-3475 compound, its mechanism of action, and reported experience with immunotherapies that have a similar mechanism of action. Special attention should be paid to AEs that may be suggestive of potential irAEs. An irAE can occur shortly after the first dose or several months after the last dose of treatment.

If an irAE is suspected, efforts should be made to rule out neoplastic, infectious, metabolic, toxin or other etiologic causes prior to labeling an adverse event as an irAE. Information on how to identify and evaluate irAEs has been developed and is included in the Pembrolizumab Event of Clinical Interest Guidance Document.Subjects who develop a Grade 2 or higher irAE should be discussed immediately with the Sponsor.

Recommendations to managing irAEs not detailed elsewhere in the protocol are detailed in Table 6.

Table 6 General Approach to Handling irAEs

irAE	Withhold/Discontinue MK-3475?	Supportive Care
Grade 1	No action	Provide symptomatic treatment
Grade 2	May withhold MK-3475	Consider systemic corticosteroids in addition to appropriate symptomatic treatment
Grade 3 and Grade 4	Withhold MK-3475 Discontinue if unable to reduce corticosteroid dose to < 10 mg per day prednisone equivalent within 12 weeks of toxicity	Systemic corticosteroids are indicated in addition to appropriate symptomatic treatment. May utilize 1 to 2 mg/kg prednisone or equivalent per day. Steroid taper should be considered once symptoms improve to Grade 1 or less and tapered over at least 4 weeks.

5.6.1.2 Supportive Care Guidelines for Pneumonitis

Subjects with symptomatic pneumonitis should immediately stop receiving MK-3475 and have an evaluation. The evaluation may include bronchoscopy and pulmonary function tests to rule out other causes such as infection.

If the subject is determined to have study drug associated pneumonitis, the suggested treatment plan is detailed in Table 7.

Table 7 Recommended Approach to Handling Pneumonitis

Study drug associated pneumonitis	Withhold/Discontinue MK-3475?	Supportive Care
Grade 1 (asymptomatic)	No action	Intervention not indicated
Grade 2	Withhold MK-3475, may return to treatment if improves to Grade 1 or resolves within 12 weeks	Systemic corticosteroids are indicated. Taper if necessary.
Grade 3 and Grade 4	Discontinue MK-3475	Systemic corticosteroids are indicated. The use of infliximab may be indicated as appropriate. Refer to the Event of Clinical Interest and Immune-related Adverse Event Guidance Document for additional recommendations.

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

- First episode of pneumonitis
    - May increase dosing interval by one week in subsequent cycles
- Second episode of pneumonitis – permanently discontinue MK-3475 if upon rechallenge subject develops pneumonitis ≥ Grade 2

5.7 Diet/Activity/Other Considerations

5.7.1 Diet

Subjects should maintain a normal diet unless modifications are required to manage an AE such as diarrhea, nausea or vomiting. Patients on vorinostat are expected to take 2 L of fluid per day.

5.7.2 Contraception

MK-3475 and vorinostat may have adverse effects on a fetus in utero. Furthermore, it is not known if MK-3475 has transient adverse effects on the composition of sperm. Non-pregnant, non-breast-feeding women may be enrolled if they are willing to use 2 methods of birth control or are considered highly unlikely to conceive. Highly unlikely to conceive is defined as 1) surgically sterilized, or 2) postmenopausal (a woman who is ≥45 years of age and has not had menses for greater than 1 year will be considered postmenopausal), or 3) not heterosexually active for the duration of the study. The two birth control methods can be either two barrier methods or a barrier method plus a hormonal method to prevent pregnancy. Subjects should start using birth control from study Visit 1 throughout the study period up to 120 days after the last dose of study therapy.

Female patients of childbearing potential must have a negative serum pregnancy test (β-hCG) within 72 hours prior to receiving the first dose of vorinostat and should either be post-menopausal, free from menses for > 2 years, surgically sterilized, or willing to use 2 reliable forms of contraception simultaneously, unless abstinence is the chosen method of contraception, starting with visit 1.

Vorinostat may have adverse effects on a fetus in utero. Furthermore, it is not known if vorinostat has transient adverse effects on the composition of sperm. Adequate contraception must be used by all patients (both male and female) and their partners during therapy with vorinostat, and for 30 days after the completion of study drug administration. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with vorinostat.

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

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study they must adhere to the contraception requirement (described above) for the duration of the study and during the follow-up period defined in section 7.2.2-Reporting of Pregnancy and Lactation to the Sponsor and to Merck. If there is any question that a subject

will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

5.7.3 Use in Pregnancy

If a subject inadvertently becomes pregnant while on treatment with MK-3475 and/or vorinostat, the subject will immediately be removed from the study. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the Sponsor and to Merck without delay and within 24 hours if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor. If a male subject impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to the Sponsor and to Merck and followed as described above and in Section 7.2.2.

It is not known if vorinostat may cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies of vorinostat in pregnant women. Results of animal studies indicate that vorinostat crosses the placenta and is found in fetal plasma at levels up to 50% of maternal concentrations. Doses up to 50 and 150 mg/kg/day were tested in rats and rabbits, respectively (~0.5 times the human exposure based on AUC0-24 hours). Treatment-related developmental effects including decreased mean live fetal weights, incomplete ossifications of the skull, thoracic vertebra, sterna, and skeletal variations (cervical ribs, supernumerary ribs, vertebral count and sacral arch variations) in rats at the highest doses of vorinostat tested. Reductions in mean live fetal weight and an elevated incidence of incomplete ossification of the metacarpals were seen in rabbits dosed at 150 mg/kg/day.

The no observed effect levels (NOELs) for these findings were 15 and 50 mg/kg/day (<0.1 times the human exposure based on AUC) in rats and rabbits, respectively. A dose related increase in the incidence of malformations of the gall bladder was noted in all drug treatment groups in rabbits versus the concurrent control. If the drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

5.7.4 Use in Nursing Women

It is unknown whether MK-3475 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.

It is not known whether vorinostat is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from vorinostat, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

5.8 Subject Withdrawal/Discontinuation Criteria

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

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

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

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

  Note: A subject may be granted an exception to continue on treatment with confirmed radiographic progression if clinically stable or clinically improved, please see Section 7.2.1.6
- Unacceptable adverse experiences as described in Section 5.2.1.2
- Intercurrent illness that prevents further administration of treatment
- Investigator's decision to withdraw the subject
- 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 treatment with MK-3475

  Note: 24 months of study medication is calculated from the date of first dose. Subjects who stop MK-3475 after 24 months may be eligible for up to one year of additional study treatment if they progress after stopping study treatment provided they meet the requirements detailed in Section 5.1.4
- Administrative reasons

The End of Treatment and Follow-up visit procedures are listed in Section 6 (Protocol Flow Chart) and Section 7.1.5 (Visit Requirements). After the end of treatment, each subject will be followed for 30 days for adverse event monitoring (serious adverse events will be collected for 90 days after the end of treatment as described in Section 7.2.3.1). Subjects who discontinue for reasons other than progressive disease will have post-treatment follow-

up for disease status until disease progression, initiating a non-study cancer treatment, withdrawing consent or becoming lost to follow-up.

After documented disease progression each subject will be followed by telephone for overall survival until death, withdrawal of consent, or the end of the study, whichever occurs first.

5.9 Subject Replacement Strategy

Replacement of Patients in DLT Period

Patients who received <90% of the MK-3475 infusion in Cycle 1 (e.g., because the infusion had to be discontinued due to an infusion reaction) and did not experience a DLT will not be taken into account in the assessment of the overall DLT rate for the phase I run in cohort and need to be replaced.

If a patient experiences a DLT in Cycle 1, study therapy may be discontinued following discussion and agreement between the Sponsor and Investigator. An alternative consideration may be dose modifications of Vorinostat and MK-3475 as described in Section 5.2.1.2 with continued therapy.

Specific procedures to be performed during the trial, as well as their prescribed times and associated visit windows, are outlined in the Trial Flow Chart - Section 6.0. Details of each procedure are provided in Section 7.0 – Trial Procedures.

5.10 Clinical Criteria for Early Trial Termination

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

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

2. Poor adherence to protocol and regulatory requirements

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

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

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

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6.0 TRIAL FLOW CHART FIRST COURSE OF TREATMENT

Trial Period:	**Treatment Cycles**									**End of Treatment**		**Post-Treatment**	
Treatment Cycle/Title:	Screening	1	2	3	4	To be repeated beyond 8 cycles				Discon	Safety Follow-up	Follow Up Visits	Survival Follow-Up
						5	6	7	8				
Scheduling Window (Days):	-28 to 1		± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days post discon	Every 8 weeks post discon	Every 12 weeks
Informed Consent	X												
Inclusion/Exclusion Criteria	X												
Demographics and Medical History	X												
Trial Treatment Administration		X	X	X	X	X	X	X	X				
Survival Status													X
Review Adverse Events		X	X	X	X	X	X	X	X	X	X		
Full Physical Examination	X												
Directed Physical Examination		X	X	X	X	X	X	X	X	X	X		
Vital Signs and Weight	X	X	X	X	X	X	X	X	X	X			
ECOG Performance Status	X	X	X	X	X	X	X	X	X	X			
Pregnancy Test – Urine or Serum β-HCG	X[a]												
PT/INR and aPTT	X												
CBC	X	X	X	X	X	X	X	X	X	X	X		
Comprehensive Serum Chemistry Panel (see 7.1.3.1)	X	X	X	X	X	X	X	X	X	X	X		
Urinalysis	X												
T3, FT4 and TSH	X												
Tumor Imaging (see section 7.1.2.6)	X				X		X						
Archival or Newly Obtained Tissue Collection (see section 7.1.2.7)	X				X								

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Trial Period:	**Treatment Cycles**									**End of Treatment**		**Post-Treatment**	
Treatment Cycle/Title:	Screening	1	2	3	4	To be repeated beyond 8 cycles				Discon	Safety Follow-up	Follow Up Visits	Survival Follow-Up
						5	6	7	8				
Scheduling Window (Days):	-28 to 1		± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days post discon	Every 8 weeks post discon	Every 12 weeks
Correlative Studies Blood Collection (see section 7.1.2.7)	X				X					X			

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6.1 TRIAL FLOW CHART SECOND COURSE OF TREATMENT

Trial Period:	**Treatment Cycles**									**End of Treatment**		**Post-Treatment**	
Treatment Cycle/Title:	Screening	1	2	3	4	To be repeated beyond 8 cycles				Discon	Safety Follow-up	Follow Up Visits	Survival Follow-Up
						5	6	7	8				
Scheduling Window (Days):	-28 to 1		± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days post discon	Every 8 weeks post discon	Every 12 weeks
Inclusion/Exclusion Criteria (See Section 5.1.4)	X												
Trial Treatment Administration		X	X	X	X	X	X	X	X				
Survival Status													X
Review Adverse Events		X	X	X	X	X	X	X	X	X	X		
Full Physical Examination	X												
Directed Physical Examination		X	X	X	X	X	X	X	X	X	X		
Vital Signs and Weight	X	X	X	X	X	X	X	X	X	X			
ECOG Performance Status	X	X	X	X	X	X	X	X	X	X			
Pregnancy Test – Urine or Serum β-HCG	X												
PT/INR and aPTT	X												
CBC	X	X	X	X	X	X	X	X	X	X	X		
Comprehensive Serum Chemistry Panel (see 7.1.3.1)	X	X	X	X	X	X	X	X	X	X	X		
Urinalysis	X												
T3, FT4 and TSH	X												
Tumor Imaging (see section 7.1.2.6)	X				X		X						
Archival or Newly Obtained Tissue Collection (see section 7.1.2.7)	X				X								
Correlative Studies Blood Collection (see section 7.1.2.7)	X				X					X			

7.0 TRIAL PROCEDURES

7.1 Trial Procedures

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

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

7.1.1 Administrative Procedures

7.1.1.1 Informed Consent

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

7.1.1.1.1 General Informed Consent

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

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.

7.1.1.2 Inclusion/Exclusion Criteria

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

7.1.1.3 Medical History

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

7.1.1.4 Prior and Concomitant Medications Review

7.1.1.4.1 Prior Medications

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

7.1.1.5 Disease Details and Treatments

7.1.1.5.1 Disease Details

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

7.1.1.5.2 Prior Treatment Details

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

7.1.1.5.3 Subsequent Anti-Cancer Therapy Status

The investigator or qualified designee will review all new anti-neoplastic therapy initiated after the 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.

7.1.1.6 Assignment of Screening Number

Patients will be assigned a screening number upon consent.

7.1.1.7 Assignment of Randomization Number

There is no randomization number.

7.1.2 Clinical Procedures/Assessments

7.1.2.1 Adverse Event (AE) Monitoring

The investigator or qualified designee will assess each subject to evaluate for potential new or worsening AEs as specified in the Trial Flow Chart and more frequently if clinically indicated. Adverse experiences will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE Version 4.0 (see Section 12.2). Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

All AEs of unknown etiology associated with MK-3475 exposure should be evaluated to determine if it is possibly an event of clinical interest (ECI) of a potentially immunologic etiology (irAE). See Section 5.6.1.1 and the separate guidance document in the administrative binder regarding the identification, evaluation and management of AEs of a potential immunological etiology.

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

7.1.2.2 Full Physical Exam

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

7.1.2.3 Directed Physical Exam

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

7.1.2.4 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 6.0). Vital signs should include temperature, pulse, respiratory rate, weight and blood pressure.

7.1.2.5 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG status (see Section 12.4) at screening, prior to the administration of each dose of trial treatment and discontinuation of trial treatment as specified in the Trial Flow Chart.

7.1.2.6 Tumor Imaging and Assessment of Disease

Radiologic assessments of measurable disease will be performed using contrast CT imaging. RECIST 1.1 and IrRC criteria will be used to assess response to therapy. Radiologic imaging will be performed every 9 weeks (63 +/- 7 days). After completion of cycle #6, the intervals between radiographic evaluations can be extended to up to 12 weeks +/- 7 days, according to the discretion of the treating physician.

Radiographic imaging (RECIST 1.1 and IrRC) will be completed at a minimum of 9 weeks (63 +/- 7 days) of starting the MK-3475 and vorinostat combination. Patients who have objective responses or stable disease will continue therapy. Patients who obtain clinical benefit from the combination will be allowed to continue therapy for a maximum of 2 years, or until progression or severe toxicity, whichever comes first.

Patients can be treated for a maximum of 2 cycles before a confirmatory scan for a CR is performed.

Patients who do not achieve a RECIST 1.1 criteria objective response at the first radiographic evaluation can continue the combination of vorinostat and MK-347 provided that they do not demonstrate clinical deterioration (defined by the following parameters and determined by the treating physician):

1. Absence of signs and symptoms of disease progression
2. No decline in ECOG performance status
3. Absence of rapid disease progression
4. Absence of progressive tumor at critical anatomical sites (e.g. cord compression) requiring urgent alternative medical intervention.

Patients who receive a confirmed CR on trial may consider discontinuation of treatment. Upon progression they can be retreated on a second course of therapy according to Table 2.1. patients who progress on the second course of therapy are off study.

7.1.2.7 Tumor Tissue Collection and Correlative Studies Blood Sampling

All patients will be required to submit archival tissue as part of study participation. In patients who do not have archival tissue, a pretreatment tumor biopsy will be performed, unless deemed contraindicated by the treating physician. Every attempt to obtain additional tumor biopsies will be performed after 3 cycles of treatment are completed. Similarly,

exceptions will be made for patients in whom the treating physician feels a repeat biopsy is contraindicated. These samples will be submitted centrally for immunohistochemical expression studies involving proteins in the PD-1 family as well as CD3, CD69 and FOXP3.

Research blood collections will be obtained for correlative research studies on the following timepoints: Prior to initiation of therapy (day 1 cycle 1), and after 3 cycles of treatment, and at treatment discontinuation or progression. We intend to perform flow cytometric evaluation of CD3, CD4, CD8, CD14, PD-1, PD-L1, PD-L2 on peripheral blood mononuclear cells.

Specimen Requirements: Submission for flow cytometry

- A 5-10 mL specimen of peripheral blood in a lavender- (EDTA) or green- (sodium heparin) tube is acceptable for each draw.

- Storage/Transport Temperature: Specimens can be transported with a cold pack or wet ice, but do not fix or freeze specimens.

- Unacceptable Conditions: Frozen specimens, specimens greater than 48 hours old, specimens fixed in formalin for flow cytometry

- Address for shipping specimens:

Attn: Katy Dougherty, Hematopathology Lead

Seattle Cancer Care Alliance

Hematopathology Laboratory G7800

825 Eastlake Ave E.

Seattle, WA 98109

7.1.3 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below.

7.1.3.1 Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

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

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Table 9 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)	Aspartate aminotransferase (AST)	Specific gravity	aPTT
Red Blood Cell Count	Lactate dehydrogenase (LDH)	Microscopic exam *(If abnormal)*	Total thriiodothyronine (T3)
Absolute Neutrophil Count	Carbon Dioxide ‡	results are noted	Free thyroxine (T4)
	(CO_2 or bicarbonate)	Urine pregnancy test †	Thyroid stimulating hormone (TSH)
	Calcium		
	Chloride		Blood for correlative studies
	Glucose		
	Potassium		
	Sodium		
	Total Bilirubin		
	Direct Bilirubin *(If total bilirubin is elevated above the upper limit of normal)*		
	Total protein		
	Blood Urea Nitrogen		

† Perform on women of childbearing potential only. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required.
‡ If considered standard of care in your region.

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

7.1.4 Other Procedures

7.1.4.1 Withdrawal/Discontinuation

When a subject discontinues/withdraws prior to trial completion, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.2 - Assessing and Recording Adverse Events. Subjects who a) attain a CR or b) complete 24 months of treatment with MK-3475 may discontinue treatment with the option of restarting treatment if they meet the criteria specified in Section 7.1.5.2.1. After discontinuing treatment following assessment of CR, these subjects should return to the site for a Safety Follow-up Visit (described in Section 7.1.5.3.1) and then proceed to the Follow-Up Period of the study (described in Section 7.1.5.4).

7.1.5 Visit Requirements

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

7.1.5.1 Screening Period

The following assessments will be performed up to 28 days prior to initiation of study treatment:

1. Full Physical Examination
2. Vital Signs and weight
3. Pregnancy test or Serum B-HCG in females of childbearing age (within 72 hours of starting therapy)
4. CBC (within 10 days of starting therapy)
5. PT/INR and aPTT (within 10 days of starting therapy)
6. Comprehensive Serum Chemistry panel (within 10 days of starting therapy)
7. Urinalysis (within 10 days of starting therapy)
8. T3, FT4 and TSH (within 10 days of starting therapy)
9. Tumor imaging of known sites of disease

7.1.5.2 Treatment Period

The following assessments will be performed on day 1 of each cycle and must be performed no more than 24 hours prior to treatment unless otherwise specified. The only exception is for day 1 when the assessments will serve as baseline assessments and can be performed up to 3 weeks prior or as otherwise specified.

1. Adverse event review
3. Directed physical examination
4. Vital signs and weight
5. ECOG performance status
5. CBC
6. Comprehensive serum chemistry panel
6. Tumor Assessments of known sites of disease (every 9 weeks; 63 +/- 7 days)

7.1.5.3 Post-Treatment Visits

7.1.5.3.1 Safety Follow-Up Visit

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

7.1.5.4 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 8 weeks (56 ± 7 days) by radiologic imaging to monitor disease status. Every effort should be made to collect information regarding disease status until the start of new anti-neoplastic therapy, disease progression, death, end of the study or if the subject begins retreatment with MK-3475 as detailed in Section 7.1.5.2.1. Information regarding post-study anti-neoplastic treatment will be collected if new treatment is initiated.

Subjects who are eligible to receive retreatment with MK-3475 according to the criteria in Section 7.1.5.2.1 will move from the follow-up phase to the Second Course Phase when they experience disease progression. Details are provided in Section 6.2 – Trial Flow Chart for Retreatment.

7.1.5.4.1 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 should be contacted by telephone every 12 weeks to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

7.2 Assessing and Recording Adverse Events

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

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

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

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

Adverse events will be recorded from the time the first dose of either vorinostat or MK-3475 is administered through 30 days following cessation of treatment and at each examination on the Adverse Event case report forms/worksheets. After 30 days, adverse events related to either MP-3475 or vorinostat will be followed until resolution or stabilization of the AE or until the beginning of a new anti-neoplastic therapy, whichever occurs first. The reporting timeframe for adverse events meeting any serious criteria is described in section 7.2.3.1.

Only adverse events that meet the following definition will be recorded.

- All grade 3 and higher adverse events
- Any adverse event the requires a dose reduction or dose delay of either MK-3475 or vorinostat
- All adverse events that meet Merck's definition of Event of Clinical Interest (refer to the separate Pembrolizumab ECI guidance document)

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

For purposes of this trial, an overdose will be defined as any dose exceeding the prescribed dose for MK-3475 by 20% over the prescribed dose. No specific information is available on

the treatment of overdose of MK-3475. In the event of overdose, MK-3475 should be discontinued and the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

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

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

An overdose for vorinostat will be defined as any dose of study drug(s) that is 10% or more over the prescribed dose per cycle as described in the study protocol. 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. The pharmacological effects may be prolonged after serum levels of active vorinostat are no longer present. It is not known if vorinostat is dialyzable. In the event of overdose, vorinostat should be held and the patient should be observed closely for signs of toxicity. As clinically indicated, appropriate supportive treatment should be provided, if applicable.

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

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

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

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

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

7.2.3.1 Serious Adverse Events

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

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

- Overdose

Refer to Table 10 for additional details regarding each of the above criteria.

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

Any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study that occurs to any subject from the time the consent is signed through 90 days following cessation of treatment, or the initiation of new anti-cancer therapy, whichever is earlier, whether or not related to Merck product, must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety.

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

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

SAE reports and any other relevant safety information are to be forwarded to the Merck Global Safety facsimile number: +1-215-993-1220

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

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

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

7.2.3.2 Events of Clinical Interest

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

Events of clinical interest for this trial include:

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

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

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

3. In the event a subject develops any of the following AEs, a detailed narrative of the event should be reported as an ECI to the Sponsor within 24 hours and to Merck Global Safety within 2 working days of the event:

   a. Grade ≥ 3 diarrhea
   b. Grade ≥ 3 colitis
   c. Grade ≥ 2 pneumonitis
   d. Grade ≥ 3 hypo- or hyperthyroidism

A separate guidance document has been provided entitled "event of Clinical Interest and Immune-Related Adverse Event Guidance Document." This document provides guidance regarding identification, evaluation and management of ECIs and irAEs. Additional ECIs are identified in this guidance document and also need to be reported to the Sponsor within 24 hours and to Merck Global Safety within 2 working days of the event.

Subjects should be assessed for possible ECIs prior to each dose. Lab results should be evaluated and subjects should be asked for signs and symptoms suggestive of an immune-

related event. Subjects who develop an ECI thought to be immune-related should have additional testing to rule out other etiologic causes. If lab results or symptoms indicate a possible immune-related ECI, then additional testing should be performed to rule out other etiologic causes. If no other cause is found, then it is assumed to be immune-related.

ECIs that occur in any subject from the date of first dose through 90 days following cessation of treatment, or the initiation of a new anticancer therapy, whichever is earlier, whether or not related to the Merck's product, must be reported within 24 hours to the Sponsor and to Merck Global Safety within 2 working days.

7.2.4 Evaluating Adverse Events

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

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

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Table 10 Evaluating Adverse Events

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

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

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

7.2.5 Sponsor Responsibility for Reporting Adverse Events

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

8.0 STATISTICAL ANALYSIS PLAN

8.1 Statistical Analysis Plan Summary

The first 6 patients enrolled in this study will constitute the phase I component of the clinical trial. All patients enrolled in the study will be analyzed for the safety and efficacy endpoints of the study.

This will be a single arm phase II study which will enroll 35 patients in Cohort 1 and 35 patients in Cohort 2. All patients enrolled in the study (both in the phase I run in and phase II expansion) will be analyzed for the safety and efficacy endpoints of the study. For both Cohorts, using a 1-sided 0.07 level (exact) test with a null hypothesis of 20% response rate to the MK-3475 and vorinostat combination, an alternative of 40%, and 89% power (exact), 11/35 (31%) responses would be considered evidence to rule out an RR of < 20%. With 35 patients, frequencies can be estimated to within 17% with 95% confidence.

8.2 Statistical Analysis Plan

Toxicities will be summarized as the number and percentage of patients with each type of toxicity. Responses will be summarized as frequencies and percentages. The Kaplan Meier methods will be used to estimate overall survival and progression free survival. Outcomes will be calculated from the date of study entry to the date of the corresponding event.

9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

9.1 Investigational Product

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

MK-3475 Clinical Supplies will be provided by Merck as summarized in Table 11.

Table 11-1 Product Descriptions

Product Name & Potency	Dosage Form
MK-3475 100 mg/ 4mL	Solution for Injection

Vorinostat materials will be provided by Merck as summarized in Table 11-2

Product Name & Potency	Dosage Form	Comments
Vorinostat 100 mg	capsule	Supplied Merck

9.2 Packaging and Labeling Information

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

9.3 Clinical Supplies Disclosure

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

9.4 Storage and Handling Requirements

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

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

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

Vorinostat capsules should be stored at room temperature (do not store above 30°C). Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published. There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

Patients should be advised against opening or crushing vorinostat capsules. Direct contact of the powder in vorinostat capsules with the skin or mucous membranes should be avoided. If such contact occurs, wash thoroughly as outlined in the references. Personnel should avoid exposure to crushed and/or broken capsules. The clinical supplies storage area at the site should be monitored by the site staff, as per the institutional guidelines, for temperature consistency with the acceptable storage temperature range as mentioned above or in the product label attached to the protocol. Documentation of temperature monitoring should be maintained.

9.5. Vorinostat suspension preparation for patients unable to swallow capsules

Patients who are gastrostomy tube dependent will take vorinostat as a suspension prepared by the investigational pharmacy. The suspension will be prepared by mixing 20 mL of Suspensol S or OraPlus with the contents of twenty 100 mg vorinostat capsules in a 4 ounce glass bottle. After shaking bottle for 3 minutes to disperse, an additional 20 mL of OraSweet will be added, again shaken to disperse. This suspension will have a final concentration of 50mg/ml and will be stable for a maximum of 2 weeks.

9.6 Returns and Reconciliation

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

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

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

10.1 Confidentiality

Patient records will be kept in a secure location at the University of Washington accessible only to research authorized personnel. The patient identity will be kept as confidential as possible as required by law. Except as required by law, the patient will not be identified by name, social security number, address, telephone number, or any other direct personal identifier. Study subjects will be assigned an ID code. Information about the code will be kept in a secure location and access limited to research study personnel. The results of this research study may be presented at scientific or medical meetings or published in scientific journals. However, the patient identity will not be disclosed. The patient's personal data which may be included in the investigator's database shall be treated in compliance with all applicable laws and regulations.

10.2 Compliance with Financial Disclosure Requirements

Compliance standards established by University of Washington will be followed.

10.3 Compliance with Law, Audit and Debarment

Compliance standards established by University of Washington will be followed.

10.4 Compliance with Trial Registration and Results Posting Requirements

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

10.5 Quality Management System

The protocol, the proposed informed consent and all forms of participant information related to the study (e.g. advertisements used to recruit participants) will be reviewed and approved by the Cancer Consortium IRB and Scientific Review Committee (SRC). Any changes made to the protocol will be submitted as a modification and will be approved by the IRB prior to implementation.

The Fred Hutchinson/University of Washington Consortium Data and Safety Monitoring Committee (DSMC) will be the monitoring entity for this study in accordance with the Cancer Consortium's Data Safety Monitoring Plan.

10.6 Data Management

The Protocol Director, or her designees, will prepare and maintain adequate and accurate participant case histories with observations and other data pertinent to the study. Original source documents should be transcribed to Case Report Forms (CRFs) and used to analyze the study data. Source documents include hospital records, clinical charts, laboratory and pharmacy records, and recorded electronic data.

All data required by the trial will be entered onto paper and electronic case report forms. Any corrections to data required into the paper case report forms must be made in such a way that the original entry is not obscured. Only designated study staff will enter data for study participants after study visits. Case report forms will be checked against source document data by study staff.

Trial oversight will be carried out by the Protocol Director, Dr. Cristina Rodriguez, and her research staff. They will meet weekly to review recently acquired data and adverse events. The data recorded within the research charts and protocol database is compared with the actual data that is available from the medical record and/or clinical histories. Data detailed in the research case report forms includes the nature and severity of all toxicities, which are also reported as described above. All investigators on the protocol will receive formal training in the ethical conduct of human research. Institutional support of trial auditing is provided in accordance with the Cancer Consortium's Data and Safety Monitoring Plan. In addition,

protocols are reviewed at least annually by the Scientific Review Committee (SRC) and the Institutional Review Board (IRB).

11.0 LIST OF REFERENCES

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12.0 APPENDICES

12.1 ECOG Performance Status

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

* As published in Am. J. Clin. Oncol.: *Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.* The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.

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

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

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

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

* As published in the European Journal of Cancer:

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

12.4 Immune Response Criteria

For all patients who experience disease progression on study, the date noted for of disease progression is the time of the scan where it is originally detected, and not the following date of the confirmatory scan.

Definitions of measurable and non-measurable disease

Measurable disease: Neoplastic masses that can be precisely measured in 2 in-plane perpendicular diameters. Both its longest diameter and its longest perpendicular must be greater than or equal to 10 mm or 2 times the axial slice thickness. Lymph nodes must have a short-axis line-length of $\geq$ 15 mm. Malignant lymph nodes must be measurable in 2 perpendicular diameters. Both its longest diameter and its longest perpendicular must be greater than or equal to 15 mm or 2 times the axial slice thickness. The quantitative endpoint will be defined as the product of the longest diameter with its longest perpendicular.

Non-measurable disease: Non-measurable lesions are those that are not suitable for quantitative assessment over time. These include:

1) Neoplastic masses that are too small to measure, because their longest uninterrupted diameter or longest perpendicular are less than 10 mm or two times the axial slice thickness.

2) Neoplastic masses whose boundaries cannot be distinguished. This includes masses which cannot be demarcated from surrounding tissue because of inadequate contrast, masses with overly complex morphology, or those with highly heterogeneous tissue composition.

3) Other types of lesions that are confidently felt to represent neoplastic tissue, but difficult to quantify in a reproducible manner. These include bone metastases, leptomeningeal metastases, malignant ascites, pleural/pericardial effusions, inflammatory breast disease, lymphangitis cutis/pulmonis, cystic lesions, ill defined abdominal masses, etc.

For irRC, only target lesions selected at baseline and measurable new lesions are taken into account.

At the baseline tumor assessment, the sum of the products of the two largest perpendicular diameters (SPD) of all **index lesions** (five lesions per organ, up to 10 visceral lesions and five cutaneous index lesions) is calculated.

At each subsequent tumor assessment, the SPD of the index lesions and of new, measurable lesions (≥5 X 5 mm; up to 5 new lesions per organ: 5 new cutaneous lesions and 10 visceral lesions) are added together to provide the total time-point **tumor burden**.

Overall response using irRC:

- **Complete Response (irCR):** Complete disappearance of all tumor lesions (whether measureable or not, and no new lesions). CR must be confirmed by repeated, consecutive assessments made no less than 4 weeks from the date first documented.
- **Partial Response (irPR):** Decrease in SPD of 50% or greater by a consecutive assessment at least 4 weeks after first documentation.
- **Stable Disease (irSD):** Failure to meet criteria for irCR or irPR, in absence of irPD.
- **Progressive Disease (irPD):** At least 25% increase in SPD relative to nadir (minimum recorded tumor burden) Confirmation by a repeat, consecutive assessment no less than 4 weeks from the data first documented.

Please note other key differences between irRC and the original WHO criteria:

New measurable lesions will be incorporated into the SPD

New non measurable lesions do not define progression but preclude irCR

Non-index lesions contribute to defining irCR (complete disappearance required).

See the Investigators Imaging Operations Manual (IIOM) for more details)

REFERENCE

IrRC for the current protocol is adopted from the following reference:

Wolchok, JD, Hoos, A, O'Day S, et al., Guidelines for the Evaluation of Immune Therapy Activity in Solid Tumors: Immune-Related Response Criteria. Clinical Cancer Research, 2009 Dec 1;15(23):7412-20. Epub 2009 Nov 24.

12.5 Vorinostat Package Insert

12.7 MK-3475 Investigator Brochure

12.8 MK-3475 Pembrolizumab Events of Clinical Interest Guidance Document