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Phase II Study of Pembrolizumab (Keytruda®) in Advanced, Unresectable Hepatocellular Carcinoma (HCC)

VERSION #	5.0
VERSION DATE	01/DEC /2017

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Professor of Medicine
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FUNDING SOURCE	Merck

Regulatory Sponsor	**Sylvester Comprehensive Cancer Center (SCCC)** **PI: Lynn Feun, MD**
Funding Source(s)	**Merck**
Investigational Agent(s)	**Pembrolizumab (Keytruda®) – provided by Merck**
Other Agent(s)	N/A
IND Status	IND or IDE #: **129017** **IND Sponsor:** Lynn Feun, MD

INVESTIGATOR AGREEMENT

I confirm that I have read this protocol, I understand it, and I will work according to this protocol and to the ethical principles stated in the latest version of the Declaration of Helsinki, the applicable ICH guidelines for good clinical practices, and the applicable federal, state, and local laws, rules, and regulations relating to the conduct of the protocol.

I have read and understand the information in the Investigators' Brochure (and/or other such pertinent safety information) regarding the risks and potential benefits.

I agree to inform all those who assist/collaborate with me in the conduct of this study of their responsibilities and obligations.

Once the protocol has been reviewed and approved by the Institutional Review Board (IRB) I understand that any change(s) made during the course of the study must also (first) be approved by the IRB prior to implementation, except when such modification is made to remove any immediate hazard(s) to the subject(s).

I certify that I and the study staff responsible, have received the requisite training to conduct this research protocol.

I agree to maintain adequate and accurate records in accordance with the University of Miami policies, federal, state and local laws and regulations.

I agree to maintain the confidentiality of all information received and/or developed in connection with this protocol.

eProst Number:	
Protocol Version Number:	Protocol Version Date:

Signature of Investigator:	Date:
Name of Investigator (printed):	Institution:

PROTOCOL REVISION HISTORY

Version #	Summary of Changes	Version Date
1.1	**(Pre-Approval Changes; Sponsor Designated)** *Contact Information* • Added University of Miami Hospital (UMH) Hepatology Collaborator "Patricia Jones, MD" *Reference Safety Information as provided in Version 10 (date: 31/AUG/2015) of Pembrolizumab Investigator's Brochure (IB)* Section 9.1.4 (Management of Agent-Specific Adverse Events): • Updated safety information for patients with melanoma based on KEYNOTE-006 (i.e. AEs of Special Interest or AEOSI) • "Clinical Trials Experience" • "Immune-Related Adverse Reactions (irAEs)" • "Identification and Treatment of irAEs" • "Infusion Reactions" • "Other Immune-Mediated Adverse Reactions": o added Guillain-Barré syndrome and vitiligo • "Immune-Mediated Pneumonitis" o Updated "pneumonitis" text *Reference Risk Language as provided in Version 1.0 (date: 03/SEP/2015) of Risk Language Template for MK-3475* Informed Consent Form (ICF) Version 1.1 (dated: 06/NOV/2015): • Updated pembrolizumab side effects	06/NOV/2015
1.2	**(Pre-Approval Changes; FDA Recommendations)** • Section 10.2 Criteria modified for ALT, AST, and bilirubin toxicity to, "if these patients have Grade 3 elevation of AST/ALT, hold therapy and resume treatment when AST/ALT returns to baseline or Grade ≤ 1. • Section 10.2 Criteria modified for bilirubin to "Toxicity does not resolve within 4 weeks of last dose or if clinically symptomatic."	05/JAN/2016

2.0	**(Post-Approval Amendment; Sponsor Designated)** *Additional Sub-Investigators:* • Beatrice Madrazo, MD • Ricardo Lenicioni, MD; • Niramol Savaraj, MD; • Monica Garcia-Buitrago, MD; • Patricia D. Jones, MD; • Peter J. Hosein, MB BS and • Cristina Herrera, ARNP *Exclusion Criteria #11:* Known history of, or any evidence of active, non-infectious pneumonitis or has a history of (non-infectious) pneumonitis that required steroids or current pneumonitis *Correlative Studies, Section 1.5* modified for research blood draw collection up to 30 mL. *Cancelation Guidelines, Section 6.1:* Modified sentence to indicate that patient may withdraw at any time. *Treatment Plan, Section 8.1:* Added "iv line will be kept open with 250 mL normal saline for the drug infusion" *Hepatic Toxicity:* Changed to resolution to 12 weeks for consistency throughout document. *Section 10.2.1* modified for HBV/HCV testing: "Patients who test negative for these hepatitis labs do not need to repeat these lab tests again, unless clinically indicated" *Section 12.2* modified HBV/HCV testing needed while on treatment "if tested positive at screening" *Section 13.1 and Sections 13.2-13.5*: modified for research blood draw collection to up to 30 ml (2 green top tubes and 1 red top tube) *Appendix F* added that "PD-L1 testing will be performed by Monica Garcia Buitrago at Jackson Memorial Hospital". Also, modified for research blood draw collection to 21 ml (2 green top tubes and 1 red top tube)	12/SEP/2016

3.0	**Post Approval Amendment (Sponsor Designated)** Revisions after letter from sponsor indicated cases of Stevens-Johnson syndrome, Toxic Epidermal Necrolysis and Immune-mediated Myocarditis. Descriptions were added to Section 9.1.4 Management of Agent-Specific adverse events and to Section 10.2 Dose modification guidelines of Pembrolizumab. **Correction of some protocol language contradictions and additional clarifications. Pages 38, 57 and 59 include updated language for procedures to assess disease progression and survival.**	22/MAR/2017
4.0	**Post Approval Amendment** Increase accrual to 35 patients to account for potential screen failures and non-evaluable patients. The goal continues to be reach 28 evaluable patients. Added additional risks brought forth by Sponsor (Merck) in their 28-Aug-2017 Risk Language document for MK-3475	25/OCT/2017
5.0	**Post Approval Amendment (Sponsor Designated)** In response to Sponsor's Dear Investigator Letter to update the Dose Modification Table.	01 DEC 2017

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ABBREVIATIONS & DEFINITIONS

Term	Abbreviation	Definition
Disease Control Rate	DCR	The proportion of patients with a confirmed complete response, partial response or stable disease (CR, PR or SD), as per RECIST v1.1.
Duration of Response	DOR	The length of time from documentation of tumor response to documented disease progression.
Overall Response Rate	ORR	The proportion of patients with a confirmed complete or partial response (CR or PR), as per RECIST v1.1.
Overall Survival	OS	The length of time from the start of treatment for a disease, that patients diagnosed with the disease are still alive.
Progression-Free Survival	PFS	The length of time during and after the treatment of a disease that a patient lives with the disease but it does not get worse.

Reference: National Cancer Institute (NCI) Dictionary of Cancer Terms
http://www.cancer.gov/dictionary

PROTOCOL SYNOPSIS

<table>
<tr><td>Protocol Title</td><td>Phase II Study of Pembrolizumab (Keytruda®) in Advanced, Unresectable Hepatocellular Carcinoma (HCC)</td></tr>
<tr><td>Targeted Patient Population</td><td>Adult subjects (age ≥18 years) with confirmed advanced hepatocellular carcinoma (HCC).</td></tr>
<tr><td>Study Design</td><td>The study will be an open-label, single-institution, non-randomized, phase II study of pembrolizumab therapy in patients with advanced HCC. Patients will be treated in three-week cycles, with intravenous (IV) administration of pembrolizumab on day 1 of each 3-week cycle.

An interim analysis is planned after 14 evaluable patients are assessed for DCR to determine whether to continue with an additional 14 more.</td></tr>
<tr><td>Treatment Schema</td><td>Pembrolizumab Treatment:
<table>
<tr><td>Cycle(s)</td><td colspan="3">1</td><td colspan="3">2</td><td colspan="3">3</td><td rowspan="4">Imaging after every 3rd cycle</td><td colspan="3">4</td><td colspan="3">5, 6, 7, etc. until progression</td></tr>
<tr><td>Week(s)</td><td>1</td><td>2</td><td>3</td><td>1</td><td>2</td><td>3</td><td>1</td><td>2</td><td>3</td><td>1</td><td>2</td><td>3</td><td>1</td><td>2</td><td>3</td></tr>
<tr><td>Day(s)</td><td>1</td><td>8</td><td>15</td><td>1</td><td>8</td><td>15</td><td>1</td><td>8</td><td>15</td><td>1</td><td>8</td><td>15</td><td>1</td><td>8</td><td>15</td></tr>
<tr><td>Pembrolizumab IV q21 days</td><td>X</td><td></td><td></td><td>X</td><td></td><td></td><td>X</td><td></td><td></td><td>X</td><td></td><td></td><td>X</td><td></td><td></td></tr>
</table></td></tr>
<tr><td>Duration of Treatment</td><td>Trial therapy will last until withdrawal of consent, disease progression and/or unacceptable toxicity, whichever occurs first. Trial therapy may last for a maximum of 2 years (24 months) if the patient shows no evidence of disease progression or intolerable toxicity.</td></tr>
<tr><td>Follow-up Required Post-Treatment</td><td>All subjects will be followed at approximately 30-days (+5 days) after the last dose of trial treatment or before the initiation of a new anti-cancer treatment, whichever occurs first.

For subjects without documented evidence of objective disease progression a telephone call to the subject and/or the subject's family may be made every 12 weeks to evaluate the patient's status until documented disease progression, death, withdrawal of consent, or end of study, whichever occurs first.</td></tr>
<tr><td>Objectives</td><td>Primary Objectives:

• To determine the disease control rate (CR, PR, or SD) and response rate (CR and PR) of pembrolizumab in patients with advanced HCC.
• To determine the safety of pembrolizumab in HCC patients.

Secondary Objective:</td></tr>
</table>

	• To determine the progression-free survival (PFS), overall survival (OS), objective response rate (ORR), and duration of response (DOR). Exploratory Objective(s): • To assess HCC tumor specimens (if available) for PD-L-1 expression, and correlate with response to therapy. • To assess immunologic markers (if serum, available) for response. • To assess changes in hepatitis B and/or hepatitis C viral titer loads with pembrolizumab treatment for HCC.
Expected Number of Patients	35
Expected Number of Centers	Single center: Sylvester Comprehensive Cancer Center (SCCC). *Note: SCCC is inclusive of the constituent satellite sites.*
Expected Duration of the Protocol	Estimated duration of the main protocol (e.g. from start of screening to last subject processed and finishing the study): 3 years. This includes long term follow-up of patients, some of whom may have durable responses to therapy. Patient accrual is expected to be completed in 1.5 years (18 months). Planned accrual goals include 10-12 subjects within 1 year.
Inclusion Criteria	1. Patients must have diagnosis of advanced hepatocellular cancer (HCC) by one of the following: a. Histopathology b. Elevated serum alpha-fetoprotein (AFP) >400 ng/ml and findings on magnetic resonance imaging (MRI) or CT scans characteristic of HCC c. Findings on triple phase MRI or CT scans characteristic of HCC in patients with cirrhosis and tumors at least 1 cm or greater, without a curative treatment option (transplant, resection, or ablation). 2. Measurable disease as defined by RECIST v1.1 (provided in Section 14.0). 3. Radiographic progression on previously treated areas (as defined by RECIST v1.1). 4. Subject refusal for sorafenib treatment or intolerance to sorafenib are also allowed (intolerance is defined as ≥28 days of sorafenib

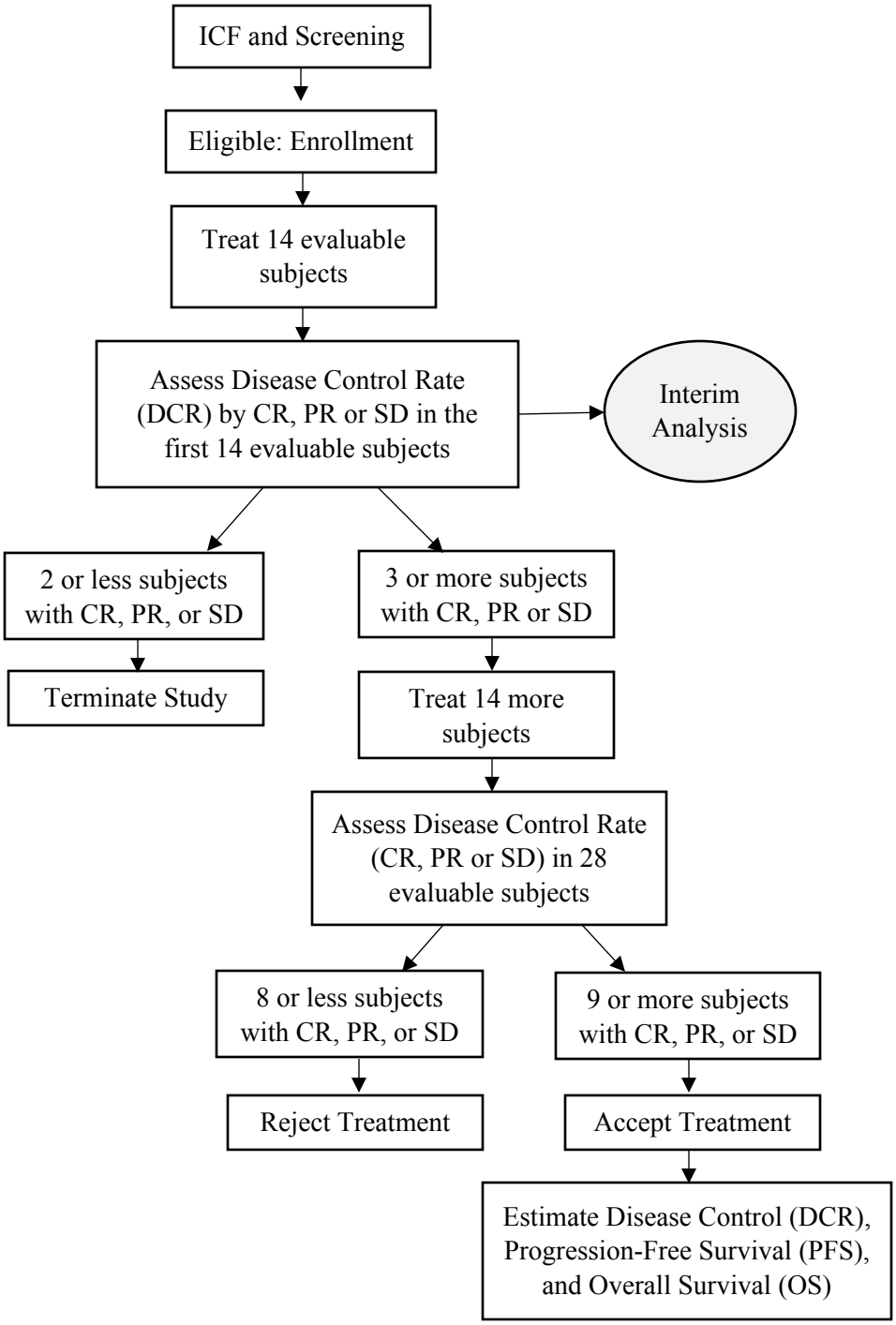
	(not necessarily consecutive) or ≥grade 3 toxicity due to sorafenib which does not resolve with appropriate supportive care). 5. Patients should have failed at least one prior systemic therapy regimen which could include sorafenib. Patients may have progressed on sorafenib, been intolerant of, or refused sorafenib. Patients who are documented to refuse systemic chemotherapy or sorafenib are also eligible. No limit to prior systemic therapy. Prior locoregional therapy such as surgery, radiofrequency ablation or transarterial chemoembolization are also allowed, provided that progression has been documented after these therapies, and ≥4 weeks have elapsed since the last therapy; (these will <u>not</u> be counted as systemic therapy). 6. Child-Pugh Classification with score ≤ 7 points. See Appendix G for criteria. 7. Age ≥ 18 years 8. Estimated life expectancy, in the judgement of the Investigator, of at least ≥ 12 weeks. 9. ECOG performance status of 0 or 1. See Appendix C. 10. Adequate bone marrow function as defined below: a. absolute neutrophil count (ANC) ≥ 1.2 x 10^9/L, b. platelets (PLT) ≥ 50 x 10^9/L 11. Adequate liver function as defined below: a. serum bilirubin < 2 mg/dl b. AST(SGOT) ≤ 5 x ULN, c. ALT(SGPT) ≤ 5 x ULN 12. Adequate coagulation as defined by: a. serum prothrombin time (PT) ≤ 16 seconds 13. Adequate renal function as defined by one of the following: a. serum creatinine ≤ 1.5 x ULN OR b. (measured or calculated) creatinine clearance ≥ 60 mL/min for patients with serum creatinine levels > 1.5 x ULN. 14. Suitable venous access to allow for all study-related blood sampling.

	15. Female subject of childbearing potential (CBP) must have a negative urine or serum pregnancy within 3 days prior to receiving the first dose of study medication. 16. Females of child bearing potential that are sexually active must agree to either practice 2 medically accepted highly effective methods of contraception at the same time *or* abstain from heterosexual intercourse from the time of signing the informed consent through 120 days after the last dose of study drug. See Appendix H for protocol-approved highly effective methods of contraceptive combinations. Subjects of childbearing potential are those who have not been surgically sterilized or have not been free from menses for > 1 year. 17. Negative test for pregnancy is required of females of child-bearing potential; A female of child bearing potential is any woman, regardless of sexual orientation or whether they have undergone tubal ligation, who meets the following criteria: a. has not undergone a hysterectomy or bilateral oophorectomy; or b. has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months or 730 days). 18. Conception while on treatment must be avoided 19. 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. 20. Ability to understand and willingness to sign a written informed consent document.
Exclusion Criteria	1. Active autoimmune disease that has required systemic treatment in the past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is <u>not</u> considered a form of systemic treatment. 2. Diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 2 years prior to the first dose of trial treatment. 3. Major surgical procedure within 28 days prior to enrollment. Note: If subject received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.

	4. Any unresolved toxicity > CTCAE grade 2 despite optimal care/support, from previous anti-cancer therapy, within 28 days prior to first dose of study drug. [Exceptions: Alopecia and ≤grade 2 neuropathy.] 5. Prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent. 6. Receipt of anti-cancer monoclonal antibody within 4 weeks prior to first dose of study drug. 7. Prior treatment with any other chemotherapy, radiotherapy, immunotherapy, or anticancer drug, agent or biologic within 4 weeks prior to first dose of study drug. 8. Has received a live vaccine within 30 days of planned start of study therapy. Note: Seasonal influenza vaccines for injection are generally inactivated flu vaccines and are allowed; however intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines, and are not allowed. 9. Receipt of any other investigational agents for their cancer ≤4 weeks of the first dose of study treatment. 10. Known history of active TB (Bacillus Tuberculosis). 11. Known history of, or any evidence of active, non-infectious pneumonitis or has a history of (non-infectious) pneumonitis that required steroids or current pneumonitis. 12. Known history of Human Immunodeficiency Virus (HIV), HIV1/2 antibodies. 13. Known hypersensitivity to pembrolizumab or any of its excipients. 14. Known active central nervous system (CNS) metastases and/or carcinomatous meningitis. [Exception: Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging, for at least 4 weeks prior to the first dose of study drug 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. This exception does not apply to carcinomatous meningitis which is excluded regardless of clinical stability.] 15. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial through 120 days after the last dose of trial treatment.

	16. Any uncontrolled, intercurrent illness including but not limited to ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, symptomatic cardiac arrhythmia. 17. Has a known additional malignancy that is progressing or requires active treatment. [Exception also include: Basal cell carcinoma of the skin or squamous cell carcinoma of the skin that has undergone potentially curative therapy, or *in situ* cervical cancer.] 18. Any other serious medical or psychiatric illness/condition likely in the judgment of the Investigator(s) to interfere or limit compliance with study requirements/treatment 19. Treatment for active HCV within 60 days of study entry. [Note: Untreated HCV positive subjects are eligible, and if stable on pembrolizumab for 6 months after study entry, consideration may be given to starting anti-HCV therapy, at the discretion of the treating Investigator.] 20. HCC patients with evidence of prior HBV must fulfill the following criteria in order to be eligible for the study: HBV VL <100 IU/mL before study enrollment, **and** subjects with active HBV need to be on anti-HBV suppression ≥3 months, throughout treatment and for at least 6 months after completion of therapy.

PROTOCOL SCHEMA



1.0 BACKGROUND

1.1 Study Disease

Hepatocellular carcinoma (HCC) is a major health problem worldwide. It is the fifth most common neoplasm in the world, and the third most common cause of cancer-related death [1]. More than 500 000 new cases are currently diagnosed yearly, with an age-adjusted worldwide incidence of 5.5 - 14.9 per 100 000 population. In some areas of Asia, HCC is the most common cause of death due to cancer. In Europe [2] and the USA [3], HCC has gained a major interest because of the rising mortality rates in the past decade (4). HCC is now the leading cause of death among patients with cirrhosis in Europe [5]. Therefore, the treatment of HCC is of great concern.

HCC's which are diagnosed at an early stage may be curable by resection, liver transplantation, or percutaneous treatment. In the West and Japan, these treatments can be applied to 30% of patients, and result in 5-year survival rates higher than 50% [6]. Resection is indicated among patients who have one tumor and well- preserved liver function. Liver transplantation benefits patients who have decompensated cirrhosis and one tumor smaller than 5 cm or three nodules smaller than 3 cm, but donor shortages limit its applicability.

Unfortunately, most HCC patients are diagnosed at an advanced stage and are not candidates for curative therapy. Until recently, there was no standard palliative therapy for patients with advanced or unresectable HCC. In 2007, the results of the SHARP trial [7] were reported. This led to the approval of sorafenib (Nexavar, Bayer-Onyx) as the first and only therapeutic agent definitively proven to prolong survival in patients with advanced HCC. Despite having a very low response rate of 2%, sorafenib improved overall survival and time to radiological progression by about 3 months compared to placebo in a Western population. The approval of sorafenib for HCC has sparked renewed enthusiasm in studying new agents in this disease for which very few options exist.

Immunotherapy is also attractive for HCC patients for several reasons: HCC is typically an inflammation-associated cancer and can be immunogenic. Cases of spontaneous regression of HCC have been reported.

Spontaneous immune responses have also been described in HCC (8,9). Activation of immune response and T-cell infiltration has been reported after percutaneous alcohol injection and radiofrequency ablation (RFA) (10).

Tumor-associated antigen (TAA)-specific CD8+ T-cell immune responses have also been reported including AFP, glypican-3, NY-ESO-1, MAGE-A and hTERT (9,11)
One report showed that HCC-infiltrating TAA-specific CD 8+ T cells were found in more than 50% of HCC patients. These cell numbers correlated with survival (12).

Other studies have shown that T regs are increased in blood and HCC tumor. These intratumoral Treg numbers also correlate with disease progression and worse prognosis (13).

Myeloid-derived suppressor cells (MDSCs) with immunosuppressive activity have also been reported to occur in the blood and tumor of HCC patients. These cells inhibit effector T cells and decrease NK cell cytotoxicity and cytokine production. MDSCs correlate with survival. It has been suggested that these cells may interact with Kupffer cells and induce PD-1 expression which will inhibit T cells (14). MDSCs can also expand the Treg population.

Recently, immunotherapy has been shown to produce antitumor effects in HCC, a tumor which has shown resistance to chemotherapy. CTLA-4 inhibition with tremelimumab was evaluated in HCV-associated HCC patients (18). Seventeen patients were evaluable for response. The disease control rate was 76.4% with 3 partial responses for 3.6, 9.2 and 15.8 months. Almost half of the stable disease patients had that status for >6 months.

At the 2015 ASCO, the preliminary results of a Phase I-II trial of PD1 (nivolumab) in advanced HCC was reported (19). Patients received nivolumab 0.1- 10 mg/kg intravenously for up to two years. The study enrolled 41 patients. Eighteen patients remained on the study and 23 discontinued treatment due to progressive disease (n=17), complete response (n=2), drug-related adverse events (AEs, n=2) and non-drug-related AEs (n=2). Drug-related AEs of any grade occurred in 29 patients (71%, 17% grade 3 or 4) with >10% of patients experiencing aspartate aminotransferase (AST) increase and rash (each 17%), alanine aminotransferase (ALT) and lipase increase (each 15%) and amylase increase (12%). Grade 3 and 4 AEs >5% were AST increase (12%), ALT increase (10%) and lipase increase (5%). A dose-limiting toxicity occurred in one patient at 10 mg/kg;no maximum tolerated dose was defined in any cohort. Response was evaluable in 39 patients: 2 CR (5%) and 7 partial response (PR 18%). Response duration was 14-17+ months for CR, <1-8 months for PR and 1.5-17+ months for stable disease. Overall survival rate at 6 months is 72%. The conclusions were that nivolumab had manageable AE profile and produced durable responses across all dose levels and HCC cohorts (no active hepatitis virus infection or virus-infected HCC), with a favorable 6-month overall survival rate.

The promising results with the tremelimumab and nivolumab trials suggest that further evaluation of immunotherapy in HCC is indicated. These also provide a rational basis to conduct further investigation into this approach.

1.2 Study Agent -Pembrolizumab (Keytruda®)

1.2.1 Pharmaceutical and Therapeutic Background

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

presence of CD8+ T-cells and the ratio of CD8+ effector T-cells / FoxP3+ regulatory T-cells seems to correlate with improved prognosis and long-term survival in many solid tumors.

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

T-cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T-cell function in peripheral tissues. Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor. PD-1 has been suggested to regulate tumor-specific T-cell expansion in subjects with melanoma (MEL). This suggests

that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and should be considered as an attractive target for therapeutic intervention.

Pembrolizumab is a potent and highly selective humanized monoclonal antibody (mAb) of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Keytruda™ (pembrolizumab) has recently been approved in the United Stated for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilumumab and, if BRAF V600 mutation positive, a BRAF inhibitor. The approved dose was 2 mg/kg iv every 3 weeks which is the dose to be used in this trial.

1.2.2 Preclinical and Clinical Trial Data from the Investigator's Brochure for Pembrolizumab (Keytruda®)

Overall Summary of Toxicology Data in Animals

The safety of pembrolizumab was characterized in the 1-month repeat-dose toxicity study in Cynomolgus monkeys when administered as IV doses of 6, 40, or 200 mg/kg once a week (a total of 5 doses) and in the 6-month repeat-dose toxicity study in Cynomolgus monkeys when administered as IV doses of 6, 40, or 200 mg/kg every other week (a total of 12 doses). Pembrolizumab was well-tolerated in Cynomolgus monkeys with a systemic exposure (AUC) of up to approximately 170,000 μg.day/mL over the course of the 1-month study and with a systemic exposure (AUC) of up to approximately 67,500 μg.day/mL over the course of the 6-month study. No findings of toxicological significance were observed in either 1-month or 6-month toxicity study with pembrolizumab, and the NOAEL was ≥200 mg/kg. In addition, no findings of toxicological relevance were observed in the *in vitro* tissue cross-reactivity study using human and Cynomolgus monkey tissues. There were no nonclinical findings that would preclude testing of pembrolizumab in clinical trials.

Efficacy Summary in Human Subjects

The P001 overall response rate (ORR) demonstrated the antitumor activity of pembrolizumab in subjects with melanoma (ipilimumab-naïve and previously treated with ipilimumab). P002 demonstrated superior PFS for both pembrolizumab treatment arms compared to the chemotherapy control arm. Treatment with pembrolizumab led to an ORR that was >4 fold higher than the response rate of the chemotherapy control arm. This difference was highly statistically significant, with a one sided p-value of <0.0001. The overall response rates for pembrolizumab treatment in P001 and P002 compared favorably to historical response rates for available treatments for melanoma, particularly in subjects who had progressed after multiple prior therapies. For example, the largest randomized clinical trial in previously treated advanced melanoma subjects, in which carboplatin and paclitaxel were used in the control arm, and

sorafenib plus carboplatin and paclitaxel in the experimental arm, produced a response rate of 11% and 12%, respectively.

Overall Adverse Events

The pembrolizumab monotherapy trials in [the] Investigator's Brochure are as follows: P001/P002, P012, P013, and P028, plus the P011 monotherapy arm. The pembrolizumab combination therapy trials in [the] section of the Investigator's Brochure are as follows: P021 and P023.

In general, the safety profile observed in P011 (monotherapy arm), P012, P013, and P028 was similar to that observed in P001/P002. In the pembrolizumab monotherapy trials, the overall incidence of AEs ranged from 83.0% (73 of 88 subjects in P013) to 100% (10 of 10 subjects in P011). In the combination therapy trials, the overall incidence of AEs was 95.4% (62 of 65 subjects) in P021 and 80% (8 of 10 subjects) in P023.

In the pembrolizumab monotherapy trials, in general, the most commonly reported AEs included fatigue, diarrhea, decreased appetite, nausea, dyspnea, and anemia. In P021, the most commonly reported AEs in this population across the dose regimens were fatigue (49.2%), constipation and nausea (26.2% each), decreased appetite (23.1%), diarrhea (18.5%), and anemia and alopecia (15.4% each). In P023, the most commonly reported AEs experienced in this population across the dose regimens were neutropenia and thrombocytopenia (50.0% each), followed by anemia, respiratory tract infection, and back pain (30.0% each).

In the pembrolizumab monotherapy trials, the incidence of drug-related AEs (DRAEs) ranged from 39.8% (35 of 88 subjects in P013) to 80.0% (8 of 10 subjects in P011). In the combination therapy trials, the incidence of DRAEs was 86.2% (56 of 65 subjects in this population) in P021 and 60.0% (6 of 10 subjects in this population) in P023. In the pembrolizumab monotherapy trials, the most commonly reported DRAEs across all studies were nausea, fatigue, and diarrhea. In P021, the most commonly reported DRAEs experienced in this population across the dose regimens were fatigue (35.4%); nausea, decreased appetite, and alopecia (13.8% each); diarrhea (12.3%); and constipation and aspartate aminotransferase increased (10.8% each). In combination therapy trial P023, the most commonly reported DRAEs experienced in this population across the dose regimens were neutropenia and thrombocytopenia (50.0% each), anemia (30.0%), dysphonia, hiccups, and pruritus (20.0% each).

In the pembrolizumab monotherapy trials, the incidence of Grade 3-5 DRAEs across studies ranged from 6.8% (6 of 88 in P013) to 12.0% (187 of 1562 subjects) in P001/P002. In the combination therapy trials, Grade 3-5 DRAEs were reported in 23.1% (15 of 65 subjects in this population) in P021 and 50.0% (5 of 10 subjects in this population) in P023.

In the pembrolizumab monotherapy trials, the most commonly reported Grade 3-5 DRAEs were anemia, alanine aminotransferase increased, aspartate aminotransferase increased, and colitis. In P021, the most common Grade 3-5 DRAEs in this population across dose regimens were aspartate aminotransferase increased (6.2%) and anemia and alanine aminotransferase increased (4.6% each). In P023, the only Grade 3-5 DRAEs that occurred in more than 1 subject in this population across dose regimens were neutropenia (40.0%) and anemia (20.0%).

In the pembrolizumab monotherapy trials, most subjects who experienced an AE continued in the study, with the incidence of AEs leading to discontinuation ranging from 4.2% (18 of 430 subjects in P028) to 12.3% (192 of 1562 subjects in P001/P002). The majority of AEs leading to discontinuation were not considered drug related. Discontinuations due to a DRAE were infrequent and ranged from 0% (no subjects in P011) to 4.5% (4 of 88 subjects in P013). The most commonly reported DRAE leading to discontinuation was pneumonitis.

In P021, most subjects continued treatment despite AEs, and only 4.6% discontinued due to an AE. Only 3.1% of subjects discontinued study treatment due to an AE that was considered related to study treatment by Investigators. Interstitial lung disease, dermatitis allergic and drug eruption were the only DRAEs resulting in discontinuation and were reported in 1 subject each (1.5%). In P023, no subjects discontinued due to an AE.

1.3 **Rationale**

1.3.1 Rationale for the Trial and Selected Subject Population

In our study, we will study a different PD 1 drug (Pembrolizumab, Merck) for advanced HCC. This drug has been approved for treatment of malignant melanoma and has shown antitumor activity in several other malignancies. We have experience with this drug in treating cancer patients here at Sylvester. Since check point inhibitors (CPI) such as tremelimumab and nivolumab have shown activity in HCC, it is reasonable to assess Pembrolizumab in advanced HCC patients.

1.3.2 Rationale for Dose Selection/ Regimen/ Modification

An open-label Phase I trial (Protocol 001) was being conducted to evaluate the safety and clinical activity of single agent MK-3475. The dose escalation portion of this trial evaluated three dose levels, 1 mg/kg, 3 mg/kg, and 10 mg/kg, administered every 2 weeks (Q2W) in subjects with advanced solid tumors. All three dose levels were well tolerated and no dose-limiting toxicities were observed. This first in human study of MK-3475 showed evidence of target engagement and objective evidence of tumor size reduction at all dose levels (1 mg/kg, 3 mg/kg and 10 mg/kg Q2W). No MTD has been identified to date. 10.0 mg/kg Q2W, was the highest dose tested in PN001. Recent data from other clinical studies

within the MK-3475 program has shown that a lower dose of MK-3475 and a less frequent schedule may be sufficient for target engagement and clinical activity.

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

A population pharmacokinetic analysis has been performed using serum concentration time data from 476 patients. Within the resulting population PK model, clearance and volume parameters of MK-3475 were found to be dependent on body weight. The relationship between clearance and body weight, with an allometric exponent of 0.59, is within the range observed for other antibodies and would support both body weight normalized dosing or a fixed dose across all body weights. MK-3475 has been found to have a wide therapeutic range based on the melanoma indication. The differences in exposure for a 200 mg fixed dose regimen relative to a 2 mg/kg Q3W body weight based regimen are anticipated to remain well within the established exposure margins of 0.5 – 5.0 for MK-3475 in the melanoma indication. The exposure margins are based on the notion of similar efficacy and safety in melanoma at 10 mg/kg Q3W vs. the dose regimen of 2 mg/kg Q3W (i.e. 5-fold higher dose and exposure). The population PK evaluation revealed that there was no significant impact of tumor burden on exposure. In addition, exposure was similar between the NSCLC and melanoma indications. Therefore, there are no anticipated changes in exposure between different indication settings.

The choice of the 200 mg Q 3W as an appropriate dose is based on simulations performed using the population PK model of pembrolizumab showing that the fixed dose of 200 mg every 3 weeks will provide exposure that 1)are optimally consistent with those obtained with the 2 mg/kg dose every 3 weeks, 2) will maintain individual patient exposures in the exposure range established in melanoma as associated with maximal efficacy response and 3) will maintain individual patients exposure in the exposure range established in melanoma that are well tolerated and safe. A fixed dose regimen will simplify the dosing regimen to be more convenient for physicians and to reduce potential for dosing errors. A fixed dosing scheme will also reduce complexity in the logistical chain and reduce wastage.

1.4 Gender and Ethnicity

There are no limitations in terms of gender or ethnicity for eligibility.

1.5 Correlative Studies

If available, tumor tissue either at time of diagnosis or archived tumor may be stained for PD-L-1 expression. In tumors such as melanoma, PD-L-1 expression is associated with higher response rate to PD-1 or PD-L-1 agents but even patients with no PD-L-1

expression may respond to these agents. To our knowledge, no data exists for HCC and PD-1 agents or PD-L-1 agents. Obtaining tumor tissue for correlative studies is optional for the patient. We will assess PD-L-1 tumor expression with clinical outcome. This is exploratory and there is no formal statistical analysis planned.

Patients who agree may have blood drawn (up to 30 mL if feasible) to perform immunologic markers (such as phenotype for T and NK cell markers by flow cytometry). Patients with hepatitis B or C will have blood (7 ml) drawn to assess viral titer load. These blood samples will be performed at baseline, every 3 weeks while on drug treatment and at the time of tumor response or progression. The purpose is to determine if immunologic markers and/or viral titers change with treatment. This is exploratory and no formal statistical analysis is planned. A descriptive analysis will be done for hypothesis-generating purposes but a statistical analysis will not be done as there may not be enough tumor tissue and blood samples collected (to conduct a formal statistical analysis).

We will also analyze several representative cytokines associated with T cell activation and suppression in serum, tumor biopsy and PBMCs from patients with pretreatment of anti-PD-1 and every 9 weeks (2-3 times) after anti-PD-1 treatment. T cell proliferation and activation in response to T cell receptor (TCR) and CD28 signals require IL-2, IL-12, IFN-r stimulation, but can be suppressed by immunosuppressive cytokines such as IL-10 and TGF-β. This is exploratory and no formal statistical analysis is planned. A descriptive analysis will be done for hypothesis-generating purposes but a statistical analysis will not be done as there may not be enough tumor tissue and blood samples collected (to conduct a formal statistical analysis).

2.0 OBJECTIVES

2.1 Primary Objectives

- To determine the disease control rate (CR, PR or SD) and response rate (CR and PR) of pembrolizumab in patients with advanced HCC.
- To determine the safety of pembrolizumab in HCC patients.

2.2 Secondary Objectives

- To determine the progression-free survival (PFS), overall survival (OS), and objective response rate (ORR) and duration of response (DOR)

2.3 Exploratory Objectives

- To assess HCC tumor specimens (if available) for PD-L-1 expression, and correlate with response to therapy.
- To assess immunologic markers (if serum, available) for response.

- To assess changes in hepatitis B and/or hepatitis C viral titer load with pembrolizumab treatment for HCC.

3.0 ENDPOINTS

3.1 Primary endpoints

- Disease control rate (DCR) will be calculated per RECIST 1.1, as the proportion of patients with best overall response of complete response (CR), partial response (PR) or stable disease (SD) that is maintained for at least 8 weeks.
- Treatment-related adverse events (AEs) including serious adverse events (SAEs). AEs will be assessed by and assigned severity using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 4.03.

3.1.1 Evaluable:

- Evaluable for DCR: Eligible subjects who receive at least one dose of pembrolizumab, have measurable disease at baseline, and have at least one post-baseline disease response assessment.
- Evaluable for Safety: Eligible subjects who receive at least one dose of pembrolizumab.

3.2 Secondary endpoints

- Progression-free survival (PFS) will be defined as the elapsed time from the first date of study treatment until documented disease progression (as per RECIST 1.1) or death from any cause, whichever is earlier. For patients who remain alive without progression, follow-up time will be censored at the date of last disease assessment (as per RECIST 1.1).
- Overall survival (OS) will be defined as the elapsed time from the first date of study treatment to death from any cause. For surviving patients, follow-up will be censored at the date of last contact (or last date known to be alive). Follow-up for OS will occur every 12 weeks (±1 month) until death or withdrawal of consent from the study.
- Objective response rate (ORR) will be defined as the proportion of the patients with a confirmed complete or partial response (CR or PR), as per RECIST 1.1.
- Duration of Response (DoR) will be defined as the elapsed time from documented tumor response to documented disease progression.

3.2.1 Evaluable for PFS, OS, ORR and DOR: Eligible subjects who receive at least one dose of pembrolizumab, have measurable disease at baseline, and have at least one post-baseline disease response assessment.

3.3 Exploratory endpoints

- The expression levels of PD-L-1 in tumor tissue, and immunologic markers as well as serum titers of hepatitis B or C in patients with hepatitis B or C, respectively, for whom specimens are available.

3.3.1 Evaluable:

- Evaluable for Tissue Correlative Study: Eligible subjects who agree to tissue sampling, receive at least one dose of pembrolizumab, have measurable disease at baseline, and have at least one post-baseline disease response assessment.
- Evaluable for Serum Correlative Study: Eligible subjects who agree to serum sampling and receive at least one dose of pembrolizumab.

4.0 SUBJECT RECRUITMENT & SCREENING

Subjects will be recruited at Sylvester Comprehensive Cancer Center via clinical practice offices. Both men and women of all races and ethnic groups are eligible for this trial.

5.0 PATIENT SELECTION

5.1 Inclusion Criteria

1	Patients must have diagnosis of advanced hepatocellular cancer (HCC) by one of the following: a) Histopathology b) Elevated serum alpha-fetoprotein (AFP) >400 ng/ml and findings on magnetic resonance imaging (MRI) or computed tomography (CT) scans characteristic of HCC c) Findings on triple phase MRI or CT scans characteristic of HCC in patients with cirrhosis and tumors at least 1 cm or greater, without a curative treatment option (transplant, resection, or ablation).
2	Measurable disease as defined by RECIST v1.1 (provided in Section 14.0).
3	Radiographic progression on previously treated areas (as defined by RECIST v1.1).
4	Subject refusal for sorafenib treatment or intolerance to sorafenib are also allowed (intolerance is defined as ≥28 days of sorafenib (not necessarily consecutive) or ≥grade 3 toxicity due to sorafenib which does not resolve with appropriate supportive care).
5	Patients should have failed at least one prior systemic therapy regimen which could include sorafenib. Patients may have progressed on sorafenib, been intolerant of, or refused sorafenib. Patients who are documented to refuse systemic chemotherapy or sorafenib are also eligible. No limit to prior systemic therapy. Prior locoregional therapy such as surgery, radiofrequency ablation or transarterial chemoembolization are also allowed, provided that progression has been documented after these therapies, and ≥4 weeks have elapsed since the last therapy; (these will not be counted as systemic therapy).
6	Child-Pugh Classification with score ≤ 7 points. See Appendix G for criteria.

7	Age ≥ 18 years
8	Estimated life expectancy, in the judgement of the Investigator, of at least ≥ 12 weeks.
9	ECOG performance status of 0 or 1. See Appendix C.
10	Adequate bone marrow function as defined below: a) absolute neutrophil count (ANC) ≥ 1.2 x 10^9/L, b) platelets (PLT) ≥ 50 x 10^9/L
11	Adequate liver function as defined below: a) serum bilirubin < 2 mg/dl b) AST(SGOT) ≤ 5 x ULN, c) ALT(SGPT) ≤ 5 x ULN
12	Adequate coagulation as defined by: a) serum prothrombin time (PT) ≤ 16 seconds
13	Adequate renal function as defined by one of the following: a) serum Creatinine ≤ 1.5 x ULN OR b) (measured or calculated) Creatinine clearance ≥ 60 mL/min for patients with serum creatinine levels > 1.5 x ULN.
14	Suitable venous access to allow for all study-related blood sampling.
15	Female subject of childbearing potential (CBP) must have a negative urine or serum pregnancy within 3 days prior to receiving the first dose of study medication.
16	Females of child bearing potential that are sexually active must agree to either practice 2 medically accepted highly effective methods of contraception at the same time *or* abstain from heterosexual intercourse from the time of signing the informed consent through 120 days after the last dose of study drug. See Appendix H for protocol-approved highly effective methods of contraceptive combinations. Subjects of childbearing potential are those who have not been surgically sterilized or have not been free from menses for > 1 year.
17	Negative test for pregnancy is required of females of child-bearing potential; A female of child bearing potential is any woman, regardless of sexual orientation or whether they have undergone tubal ligation, who meets the following criteria: a) has not undergone a hysterectomy or bilateral oophorectomy; or b) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months or 730 days).
18	Conception while on treatment must be avoided
19	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.
20	Ability to understand and willingness to sign a written informed consent document.

5.2 **Exclusion Criteria**

1	Active autoimmune disease that has required systemic treatment in the past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.
2	Diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 2 years prior to the first dose of trial treatment.
3	Major surgical procedure within 28 days prior to enrollment. Note: If subject received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.
4	Any unresolved toxicity > CTCAE grade 2 despite optimal care/support, from previous anti-cancer therapy, within 28 days prior to first dose of study drug. [Exceptions: Alopecia and ≤grade 2 neuropathy.]
5	Prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent.
6	Receipt of anti-cancer monoclonal antibody within 4 weeks prior to first dose of study drug.
7	Prior treatment with any other chemotherapy, radiotherapy, immunotherapy, or anticancer drug, agent or biologic within 4 weeks prior to first dose of study drug.
8	Has received a live vaccine within 30 days of planned start of study therapy. Note: Seasonal influenza vaccines for injection are generally inactivated flu vaccines and are allowed; however intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines, and are not allowed.
9	Receipt of any other investigational agents for their cancer ≤4 weeks of the first dose of study treatment.
10	Known history of active TB (Bacillus Tuberculosis).
11	Known history of, or any evidence of active, non-infectious pneumonitis or has a history of (non-infectious) pneumonitis that required steroids or current pneumonitis.
12	Known history of Human Immunodeficiency Virus (HIV), HIV1/2 antibodies.
13	Known hypersensitivity to pembrolizumab or any of its excipients.
14	Known active central nervous system (CNS) metastases and/or carcinomatous meningitis. [Exception: Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging, for at least 4 weeks prior to the first dose of study drug 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. This exception does not apply to carcinomatous meningitis which is excluded regardless of clinical stability.]

15	Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial through 120 days after the last dose of trial treatment.
16	Any uncontrolled, intercurrent illness including but not limited to ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia.
17	Has a known additional malignancy that is progressing or requires active treatment. [Exception: Basal cell carcinoma of the skin or squamous cell carcinoma of the skin that has undergone potentially curative therapy, or *in situ* cervical cancer.]
18	Any other serious medical or psychiatric illness/condition likely in the judgment of the Investigator(s) to interfere or limit compliance with study requirements/treatment.
19	Treatment for active HCV within 60 days of study entry. [Note: Untreated HCV positive subjects are eligible, and if stable on pembrolizumab for 6 months after study entry, consideration may be given to starting anti-HCV therapy, at the discretion of the treating Investigator.]
20	HCC patients with evidence of prior HBV must fulfill the following criteria in order to be eligible for the study: HBV VL <100 IU/mL before study enrollment, **and** subjects with active HBV need to be on anti-HBV suppression ≥3 months, throughout treatment and for 6 months after.

6.0 Enrollment Procedures

To enter a patient, the Investigator or Study Team will contact the Clinical Research Services' (CRS) Representative. All eligibility requirements must be reviewed prior to the patient entering the study. The following information must be provided to the CRS Representative:

1) Completed and signed protocol-specific eligibility checklist;
2) All pages of the original signed informed consent form (ICF) including HIPAA Form B;
3) Relevant source documents including but not limited to: subject medical history and physical exam, concomitant medications, admission or discharge notes, diagnostic reports, pathologic confirmation of diagnosis, and relevant subject-specific written communication.

6.1 Cancellation Guidelines

Patient may withdraw from the study at any time. Contact the CRS Representative, or e-mail the information including the reasons for withdrawal within 10-business days.

7.0 STUDY DESIGN

The study will be an open-label, single-institution, non-randomized, single-arm, Phase II study of pembrolizumab therapy in patients with advanced HCC. Patients will be treated in three-week cycles, with intravenous (IV) administration of pembrolizumab on day 1 of each 3-week cycle. Trial therapy will last until withdrawal of consent, disease progression and/or unacceptable toxicity, whichever occurs first.

Correlative studies investigating PD-L-1 expression in tumor tissue will be assessed with clinical outcome. Peripheral blood will also be drawn to perform immunologic markers and hepatitis B or C viral titers. This is to determine if viral titers change with treatment. These studies are included for all patients who consent to the correlative studies (See Appendix F). There is an additional consent for the correlative studies.

Up to 28 evaluable patients will be enrolled at Sylvester Comprehensive Cancer Center (SCCC). We expect to enroll 10-12 patients per year based on our institution's enrollment capacity. Expected time to complete total accrual is approximately 1.5 years. Expected time to study completion is 3 years from date open to enrollment to allow for survival data. An interim analysis is planned after 14 evaluable patients are assessed for DCR to determine whether to continue with an additional 14 more.

8.0 TREATMENT PLAN

8.1 Pembrolizumab (Keytruda®)

Pembrolizumab 200 mg shall be administered in the outpatient setting as a 30 minute intravenous (IV) infusion, once every 21 days. The intravenous line should contain a sterile, non-pyrogenic, low-protein binding 0.2 micron to 5 micron in-line or add-on filter. Do not co-administer other drugs through the same infusion line. Every effort to target infusion timing to be as close to 30 minutes as possible, should be made. The iv line will be kept open with 250 ml normal saline for the drug infusion. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (i.e. infusion time is 30 minutes: -5 min/+10min).

For additional information on pembrolizumab including mechanism of action, drug metabolism, pharmacokinetics & toxicology, known side effects, composition, and storage recommendations, see Section 9.0.

8.2 Treatment Schema

Regimen Description					
Agent	***Premedications; Precautions***	***Dose***	***Route***	***Schedule***	***Cycle Length***
Pembrolizumab	*Grade 2 infusion reactions will be premedicated with diphenhydramine 50 mg IV and acetaminophen 500-1000 mg PO prior to subsequent infusions.* *Diet: Subjects should maintain a normal diet unless modifications are required to manage an AE such as diarrhea, nausea or vomiting.*	*200 mg*	*IV infusion over 30 minutes (-5min/ +10min)*	*Day 1 (±3), every 3 weeks*	*21 days* *(3 weeks)*

8.3 Treatment Dispensation, Compliance and Accountability

Eligible subjects shall be treated with the investigational supply of pembrolizumab. Clinical supplies may not be used for any purpose other than that stated in the protocol.

Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements. Drug identity (name, strength) is included in the label text. Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label.

Receipt and dispensing of investigational product must be recorded by authorized person(s) at the trial site. The Investigator is responsible for maintaining accurate records of the clinical supplies received from Merck, the amount dispensed to 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 the 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.

8.4 Supportive Care Guidelines

Subjects should receive appropriate supportive care measures as deemed necessary by the treating Investigator. Suggested supportive care measures for the management of adverse events (AEs) with potential immunologic etiology are outlined below. Where

appropriate, these guidelines include the use of oral or intravenous treatment with corticosteroids as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids.

Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care.

It may also become necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event. Suggested conditional procedures for Events of Clinical Interest (ECI) associated with pembrolizumab, can be found in Appendix I.

The treatment guidelines are intended to be applied when the Investigator(s) determine the events to be related (possible, probable or definite) to trial treatment. Note: if after an evaluation the event is determined not to be related to the trial treatment, the Investigator is instructed to follow the reporting guidance in Appendix A (and Section 15.0). Refer to Section 10.0 for dose modification(s).

8.4.1 Concomitant Medications/ Vaccinations

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

[Exception: Eligible HCC patients with HBV must be on anti-HBV suppression throughout treatment and for 6 months after the end of treatment.]

8.4.1.1. Acceptable Concomitant Medications

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

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

8.4.1.2. Prohibited Concomitant Medications

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

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab
- Radiation therapy
  Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed at the investigator's discretion.
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine.
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.
- Treatment for hepatitis C within 60 days of study entry. Note: If stable on pembrolizumab for 6 months after study entry, consideration may be given to start anti-HCV therapy, at the discretion of the treating Investigator.

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 (Section 5.2) describes other medications which are prohibited in this trial.

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

8.5 Duration of Treatment

Trial therapy will last until withdrawal of consent, disease progression, after CR (as specified below), and/or unacceptable toxicity, whichever occurs first. Trial therapy may last for a maximum of 2 years (24 months) if the patient shows no evidence of disease progression or intolerable toxicity.

8.6 Duration of Follow-Up

All subjects will be followed at approximately 30-days (+5 days) after the last dose of trial treatment or before the initiation of a new anti-cancer treatment, whichever occurs first.

Every effort should be made to collect information regarding disease status until disease progression, withdrawal of consent, death, end of the study (EoS) or if new anti-neoplastic treatment is initiated.

For patients without documented evidence of objective disease progression the following assessments should be performed every 12 weeks until documented disease progression, death, withdrawal of consent, or end of study, whichever occurs first. A telephone call to the patient and/or the patient's family may be made to evaluate the patient's status on the following:

- Post-study anticancer therapy status
- Survival status"

Following confirmed disease progression or initiation of new anti-cancer therapy, survival will be assessed (at a minimum) by telephone contact every 12 weeks (±2 weeks).

Following confirmed disease progression or initiation of new anti-cancer therapy, survival will be assessed (at a minimum) by telephone contact every 12 weeks (±2 weeks).

See Section 12.4 and 12.5 for further details on Follow-Up assessments.

9.0 AGENTS (DRUG FORMULATION AND PROCUREMENT)

9.1 Pembrolizumab

[Refer to the FDA-approved package insert and most current version of the Investigator's Brochure for more information.]

9.1.1 Other name(s)

MK-3475, Keytruda ®

9.1.2 Mechanism of Action

MK-3475 is a potent and highly selective humanized mAb designed to block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. MK-3475 potently blocks binding to both ligands with half maximal inhibitory concentration (IC50) values below 1 nM. MK-3475 enhances T cell responses in human donor blood cell cultures with an EC50 of ~0.1 to 0.3 nM. MK-3475 binds to cynomolgus PD-1 with similar affinity, blocking activity, and demonstrates equivalent enhancement of cynomolgus T cell responses. It does not cross-react with rodent PD-1. MK-3475 strongly enhances T lymphocyte immune responses in cultured blood cells from healthy human donors, cancer patients, and primates. The antibody potentiates existing immune responses only in the presence of antigen-receptor stimulation and does not nonspecifically activate all T cells. Using an anti-mouse

PD-1 analog antibody, PD-1 blockade is demonstrated to significantly inhibit tumor growth in a variety of syngeneic murine tumor models. In experiments in mice, anti-PD-1 therapy is synergistic with chemotherapeutic agents such as gemcitabine and 5-FU and combination therapy results in increased efficacy and increased complete regression rates *in vivo*.

9.1.3 Drug Metabolism, Pharmacokinetics and Toxicology

The pharmacokinetics of pembrolizumab was studied in 479 patients who received doses of 1 to 10 mg/kg every 2 weeks or 2 to 10 mg/kg every 3 weeks. Based on a population pharmacokinetic analysis, the mean [% coefficient of variation (CV%)] clearance (CL) is 0.22 L/day (28%) and the mean (CV%) elimination half-life (t1/2) is 26 days (24%). Steady-state concentrations of pembrolizumab were reached by 18 weeks of repeated dosing with an every 3-week regimen and the systemic accumulation was 2.1-fold. The peak concentration (Cmax), trough concentration (Cmin), and area under the plasma concentration versus time curve at steady state (AUCss) of pembrolizumab increased dose proportionally in the dose range of 2 to 10 mg/kg every 3 weeks. In animal models, inhibition of PD-1 signaling resulted in an increased incidence of infections and enhanced inflammatory responses. M. tuberculosis-infected PD-1 knockout mice exhibit markedly decreased survival compared with wild-type controls, which correlated with increased bacterial proliferation and inflammatory responses in these animals. PD-1 knockout mice have also shown decreased survival following infection with lymphocytic choriomeningitis virus (LCMV). Administration of pembrolizumab in chimpanzees with naturally occurring chronic hepatitis B infection resulted in two out of four animals with significantly increased levels of serum ALT, AST, and GGT, which persisted for at least 1 month after discontinuation of pembrolizumab.

9.1.4 Management of Agent-Specific Adverse Events

There are no specific safety concerns based on the results of nonclinical studies. Pembrolizumab has the same mechanism of action as other anti–PD-1 monoclonal antibodies. Preclinical studies have suggested similar potency, and pharmacokinetic (PK) modeling has suggested similar human PK in the class. Accordingly, the AEs observed with other anti–PD-1 antibodies may serve as an indicator for the AEs to expect in cancer subjects. Furthermore, AEs from other immunotherapies for cancer were considered in the Pembrolizumab Program (MK-3475) Event of Clinical Interest (ECI) Guidance Document.

Pembrolizumab is generally well tolerated and demonstrates a favorable safety profile in comparison to chemotherapy. Pembrolizumab is an immunomodulatory agent, and based on this mechanism of action, immune mediated adverse events are of primary concern.

Important identified risks for pembrolizumab are of an immune mediate nature, including: pneumonitis, colitis, thyroid disorders (hypothryoidism/ hyperthyroidism), hepatitis, hypophysitis, Type I diabetes mellitis, uveitis, and

nephritis. After a recent review of data, events newly characterized as identified risks also include pancreatitis, myositis, and severe skin reaction; these are included in the reference safety information below. The majority of immune-mediated adverse events were mild to moderate in severity, were manageable with appropriate care, and rarely required discontinuation of therapy. Further details around frequency, reporting, and management of immune-related adverse events (irAEs) are described below. In addition to the previously noted identified risks, infusion-related reactions are a risk but are not considered immune mediated; these are further described below.

Clinical Trials Experience

The safety of KEYTRUDA was investigated in two controlled, randomized studies (KEYNOTE-002 and KEYNOTE-006) for the treatment of unresectable or metastatic melanoma and in an uncontrolled, open-label study (KEYNOTE-001) for the treatment of unresectable or metastatic melanoma and metastatic non-small cell lung carcinoma (NSCLC). Overall, 1567 subjects with melanoma (699 previously treated with ipilimumab and 868 naïve to ipilimumab) and 550 subjects with NSCLC were treated. Safety is described for the pooled population of 2117 subjects (studied across three doses; 2 mg/kg every 3 weeks and 10 mg/kg every 2 or 3 weeks). The median treatment duration was 4.6 months (range 1 day to 28.3 months) including 906 subjects treated for greater than or equal to 6 months and 203 subjects treated for greater than or equal to one year.

KEYTRUDA was discontinued for treatment-related adverse reactions in 4% of subjects. Treatment-related serious adverse events (SAEs) reported up to 90 days after the last dose occurred in 9% of subjects receiving KEYTRUDA. Of these treatment-related SAEs, those occurring in more than five subjects (out of 2117) were pneumonitis (n=24), colitis (n=19), diarrhea (n=16), pyrexia (n=8), adrenal insufficiency (n=6) and autoimmune hepatitis (n=6).

Immune-Related Adverse Events (irAEs)

An irAE is defined as a clinically significant AE of any organ that is associated with study drug exposure, is of unknown etiology, and is consistent with an immune-related mechanism. AEs of Special Interest (AEOSI) data for melanoma and lung subjects demonstrates that irAEs were reported in 16.1% of subjects (251 of 1562) overall; AEOSI were considered by the Investigators to be drug related in 14.3% of subjects (223 of 1562). The majority of AEOSI were Grade 1 or 2 in severity. Overall, serious AEOSI occurred in 4.2% of subjects at 2 mg/kg Q3W, 3.7% of subjects at 10 mg/kg Q3W, and 3.9% of subjects at 10 mg/kg Q2W. There was one AEOSI (pneumonitis) related to death in 10 mg/kg Q3W arm, in a subject with NSCLC.

The rate of discontinuation due to AEOSI was low (2.6%). The most commonly reported immune-related adverse events across the dose schedules are

hypothyroidism (7.2%), pneumonitis (2.9%), hyperthyroidism (2.2%), colitis (1.3%) and skin AEOSI (1.3% including all terms). Based on the mechanism of action of MK-3475 and similar immunomodulatory agents, the Sponsor is interested in potential irAEs, and encourages appropriate investigation of signs and symptoms suggestive of these.

Consultation with the appropriate medical specialist should be considered when investigating a possible irAE. These events can occur after the first dose to several months after the last dose of treatment. Mild irAEs are usually treated symptomatically and do not require dosing delays or discontinuation. Higher grade and persistent lower grade irAEs typically necessitate withholding or discontinuing treatment and administration of systemic steroids or other immunosuppressive agents (such as tumor necrosis factor blockers), when systemic steroids are not effective. Early recognition of irAEs and initiation of treatment are critical to reduce the risk of complications, since the majority of irAEs are reversible with the use of steroids and other immune suppressants.

Identification and Treatment of irAEs

If an irAE is suspected, a thorough evaluation should be conducted in an effort to possibly rule out neoplastic, infectious, metabolic, toxin or other etiologic causes prior to diagnosing an irAE. Serological, immunological, and histological (biopsy) data should be considered to support the diagnosis of an immune-related toxicity.

A separate document entitled Pembrolizumab Program (MK-3475) Event of Clinical Interest Guidance Document is maintained and distributed to investigational sites along with this IB and study protocols. Please refer to this guidance document in conjunction with this IB when assessing irAEs. Updates and modifications to the irAE guidance document will be made and distributed to Investigators to provide the most current information, and therefore will be independent of the IB update cycle.

It is possible that irAEs other than those listed in the guidance document may be observed in subjects receiving pembrolizumab; therefore, all AEs of unknown etiology associated with drug exposure should be evaluated to determine if it is possibly immune related. This is meant to be a general guidance; therefore, recommendations in the current document might not be all inclusive. As such Investigators are encouraged to contact a Merck Clinical Monitor as needed to discuss cases that warrant separate discussion outside of the scope of current guidelines. Permanent discontinuation of pembrolizumab due to irAE may be subject of discussion between the SPONSOR and treating Investigator. The general approach to handling irAEs can be found in Appendix I.

All AEs are to be graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.0 (http://ctep.cancer.gov).

If an irAE does not resolve or improve to ≤ Grade 1 (or to Grade 2 for ALT or AST) within 12 weeks from the start of grade 2 toxicity (or start of grade 3 toxicity for AST, ALT) study therapy discontinuation should be considered at the PI discretion or after discussion with a Merck Clinical Director.

Infusion Reactions
Infusion reactions have been reported with pembrolizumab at a rate of 2.5%; these were generally Grade 1 and 2 and the majority were considered related by the Investigator. One event of Grade 4 anaphylaxis has been reported. Infusion reactions may present as allergic reaction, serum sickness, infusion reaction, cytokine release syndrome, or anaphylaxis. Mild infusion reactions can generally be treated with interruption of the infusion and medical intervention including IV fluids, antihistamines, nonsteroidal anti-inflammatory drugs, acetaminophen, and narcotics as needed. More severe or life thereatening reactions may require pressors, corticosteroids, and epinephrine. Pembrolizumab therapy should not be redosed in these more severe cases.

Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN)
One fatal case of SJS in a clinical trial and one fatal case of TEN in the post-marketing setting have been reported in patients treated with Pembrolizumab. In total 8 cases of SJS and 2 cases of TEN all of which were serious. The risk of SJS and TEN is reported at approximately 0.4 – 7 cases per million patient years in the general adult population. Independent risk factors include certain medications such as anticolvulsants, sulfonamines, aminopenicillins, allopurinol and NSAIDs. Non-medication triggers include infection, contrast media, and vaccinations. Malignancy is associated with an increased mortality rate in patients with SJS and TEN.
Monitor patients for signs and symptoms of SJS and/or TEN, withhold Pembrolizumab and refer patient for specialized care and treatment. Administer corticosteroids for SJS grade 3 or 4 or TEN grade 4 (initial dose of 1-2 mg/kg/day prednisone or equivalent followed by a taper). Permanently discontinue Pembrolizumab for any grade of SJS or TEN.

Immune-Mediated Myocarditis
A total of 6 cases of myocarditis have been reported in patients treated with Pembrolizumab in clinical trials or in expanded access program. One fatal case was reported from a clinical trial. Immune-mediated myocarditis should be suspected if other causes of myocarditis, such as infection or prior radiation therapy, have been excluded. Risk factors include certain medications and treatment modalities such as radiation, anthracycline, alkylating agents and most recently checkpoint inhibitors.

Monitor patients for signs and symptoms of Immune-Mediated Myocarditis and ensure adequate evaluation to exclude the other ethiologies. Administer corticosteroids for grade 2 immune-mediated myocarditis (initial dose of 1-2 mg/kg/day prednisone or equivalent followed by a taper). Permanently discontinue Pembrolizumab for grade 3-4 myocarditis or if toxicity does not resolve within 12 weeks of start of grade 2 toxicity or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.

Immune-Mediated Pneumonitis

Pneumonitis occurred in 12 (2.9%) of 411 melanoma patients, including Grade 2 or 3 cases in 8 (1.9%) and 1 (0.2%) patients, respectively, receiving KEYTRUDA in Trial 1. The median time to development of pneumonitis was 5 months (range 0.3 weeks-9.9 months). The median duration was 4.9 months (range 1 week-14.4 months). Five of eight patients with Grade 2 and the one patient with Grade 3 pneumonitis required initial treatment with high-dose systemic corticosteroids (greater than or equal to 40 mg prednisone or equivalent per day) followed by a corticosteroid taper. The median initial dose of high-dose corticosteroid treatment was 63.4 mg/day of prednisone or equivalent with a median duration of treatment of 3 days (range 1-34) followed by a corticosteroid taper. Pneumonitis led to discontinuation of KEYTRUDA in 3 (0.7%) patients. Pneumonitis completely resolved in seven of the nine patients with Grade 2-3 pneumonitis.

Pneumonitis (including fatal cases) has been reported in subjects receiving KEYTRUDA. Monitor patients for signs and symptoms of pneumonitis. Evaluate patients with suspected pneumonitis with radiographic imaging and administer corticosteroids for Grade 2 or greater pneumonitis (initial dose of 1-2 mg/kg/day prednisone or equivalent followed by a taper). Withhold KEYTRUDA for moderate (Grade 2) pneumonitis, and permanently discontinue KEYTRUDA for severe (Grade 3), life-threatening (Grade 4) or recurrent moderate (Grade 2) pneumonitis. (See Immune-mediated adverse reactions below.)

Immune-Mediated Colitis

Colitis (including microscopic colitis) occurred in 4 (1%) of 411 patients, including Grade 2 or 3 cases in 1 (0.2%) and 2 (0.5%) patients, respectively, receiving KEYTRUDA in Trial 1. The median time to onset of colitis was 6.5 months (range 2.3-9.8). The median duration was 2.6 months (range 0.6 weeks-3.6 months). All three patients with Grade 2 or 3 colitis were treated with high-dose corticosteroids (greater than or equal to 40 mg prednisone or equivalent per day) with a median initial dose of 70 mg/day of prednisone or equivalent; the median duration of initial treatment was 7 days (range 4-41), followed by a corticosteroid taper. One patient (0.2%) required permanent discontinuation of KEYTRUDA due to colitis. All four patients with colitis experienced complete resolution of the event. Monitor patients for signs and symptoms of colitis. Administer corticosteroids for Grade 2 or greater colitis. Withhold KEYTRUDA for moderate (Grade 2) or severe (Grade 3) colitis, and permanently discontinue KEYTRUDA for life-threatening (Grade 4) colitis.

Immune-Mediated Hepatitis

Hepatitis (including autoimmune hepatitis) occurred in 2 (0.5%) of 411 patients, including a Grade 4 case in 1 (0.2%) patient, receiving KEYTRUDA in Trial 1. The time to onset was 22 days for the case of Grade 4 hepatitis which lasted 1.1 months. The patient with Grade 4 hepatitis permanently discontinued KEYTRUDA and was treated with high-dose (greater than or equal to 40 mg prednisone or equivalent per day) systemic corticosteroids followed by a corticosteroid taper. Both patients with hepatitis experienced complete resolution of the event.

Elevated transaminases and alkaline phosphatase may be seen during treatment. Treatment should be interrupted when transaminase or alkaline phosphatase increases are accompanied by Grade 3 total bilirubin, and/or Grade 3 coagulation tests (e.g., International Normalized Ratio [INR]), or if subjects are clinically symptomatic.

Evaluation of subjects with elevated transaminases, bilirubins, and alkaline phosphatase should involve a workup to assess for infection (SBP or other), viral reactivation (if relevant), vascular thrombosis, biliary obstruction, possible hepatotoxic medications, tumor progression, alcohol toxicity, and effects of pembrolizumab. At baseline, all subjects should be assessed for HBsAg, HBsAb, anti-HBc antibody, HBeAg, and anti-HCV. As described above, a viral load <100 IU/mL is required for study entry, and with active HBV must have also been treated with antiviral therapy for ≥3 months before initiation of study treatment. Subjects with controlled HBV on therapy should stay on this same therapy throughout pembrolizumab treatment. Subjects who are positive for HBsAg or anti-HBc (but negative for HBsAg and HBV DNA), should be assessed for HBV viral load, HBsAg, HBsAb, anti-HBc antibody, HBeAg every 3 weeks, independent of treatment delays.

Subjects with chronic infection by hepatitis C virus (HCV) with successful treatment (defined as SVR12 or SVR24) may be included. HCV genotype should also be recorded at baseline. Untreated HCV positive subjects are eligible, and if stable after 6 months on pembrolizumab, additional antiviral treatment for HCV may be considered per local standard of care. Viral loads should be assessed for those with an underlying viral etiology q 3 weeks. They should also be checked if there is an elevation in ALT >3× baseline, a tenfold or greater increase in HBV or HCV DNA > baseline, or an absolute increase in HBV or HCV DNA > 10^5 c/mL. If evidence of reactivation is present, the Sponsor should be consulted within 24 hours, and pembrolizumab treatment should be interrupted. A hepatology consult should be obtained.

- For **Grade 2** AST/ALT or alkaline phosphatase events (if normal or Grade 1 at baseline) and no other etiology is found, monitor liver function tests weekly.

- For **Grade 3-4** AST/ALT, alkaline phosphatase events if normal at baseline), or >3× baseline (if greater than 2×ULN at baseline) and no other underlying etiology is found, consider treatment with intravenous corticosteroids for 24–48 hours. When improved to baseline (for those with levels ≥2×ULN at baseline) or Grade 1 or less (for those with normal baseline values), a steroid taper should be started and continued over no less than 4 weeks.
- For **Grade 2-3** total bilirubin or PT/INR, pembrolizumab should be interrupted and steroids given as above. If values don't improve within 12 weeks from date of diagnosis of grade 3 toxicity to baseline or Grade 0-1, pembrolizumab should be permanently discontinued.
- For **Grade 4** total bilirubin or PT/INR, pembrolizumab should be permanently discontinued.

Immune-Mediated Hypophysitis
Hypophysitis occurred in 2 (0.5%) of 411 patients, consisting of one Grade 2 and one Grade 4 case (0.2% each), in patients receiving KEYTRUDA in Trial 1. The time to onset was 1.7 months for the patient with Grade 4 hypophysitis and 1.3 months for the patient with Grade 2 hypophysitis. Both patients were treated with high-dose (greater than or equal to 40 mg prednisone or equivalent per day) corticosteroids followed by a corticosteroid taper and remained on a physiologic replacement dose. Monitor for signs and symptoms of hypophysitis. Administer corticosteroids for Grade 2 or greater hypophysitis. Withhold KEYTRUDA for moderate (Grade 2) hypophysitis, withhold or discontinue KEYTRUDA for severe (Grade 3) hypophysitis, and permanently discontinue KEYTRUDA for lifethreatening (Grade 4) hypophysitis.

Renal Failure and Immune-Mediated Nephritis
Nephritis occurred in 3 (0.7%) patients, consisting of one case of Grade 2 autoimmune nephritis (0.2%) and two cases of interstitial nephritis with renal failure (0.5%), one Grade 3 and one Grade 4. The time to onset of autoimmune nephritis was 11.6 months after the first dose of KEYTRUDA (5 months after the last dose) and lasted 3.2 months; this patient did not have a biopsy. Acute interstitial nephritis was confirmed by renal biopsy in two patients with Grades 3-4 renal failure. All three patients fully recovered renal function with treatment with high-dose corticosteroids (greater than or equal to 40 mg prednisone or equivalent per day) followed by a corticosteroid taper.
Monitor patients for changes in renal function. Administer corticosteroids for Grade 2 or greater nephritis. Withhold KEYTRUDA for moderate (Grade 2) nephritis, and permanently discontinue KEYTRUDA for severe (Grade 3), or life-threatening (Grade 4) nephritis.

Immune-Mediated Hyperthyroidism and Hypothyroidism

Hyperthyroidism occurred in 5 (1.2%) of 411 patients, including Grade 2 or 3 cases in 2 (0.5%) and 1 (0.2%) patients, respectively, receiving KEYTRUDA in Trial 1. The median time to onset was 1.5 months (range 0.5-2.1). The median duration was 2.8 months (range 0.9 to 6.1). One of two patients with Grade 2 and the one patient with Grade 3 hyperthyroidism required initial treatment with high-dose corticosteroids (greater than or equal to 40 mg prednisone or equivalent per day) followed by a corticosteroid taper. One patient (0.2%) required permanent discontinuation of KEYTRUDA due to hyperthyroidism. All five patients with hyperthyroidism experienced complete resolution of the event. Hypothyroidism occurred in 34 (8.3%) of 411 patients, including a Grade 3 case in 1 (0.2%) patient, receiving KEYTRUDA in Trial 1. The median time to onset of hypothyroidism was 3.5 months (range 0.7 weeks-19 months). All but two of the patients with hypothyroidism were treated with long-term thyroid hormone replacement therapy. The other two patients only required short-term thyroid hormone replacement therapy. No patient received corticosteroids or discontinued KEYTRUDA for management of hypothyroidism. Thyroid disorders, including thyroiditis, can occur at any time during treatment. Monitor patients for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders. Administer corticosteroids for Grade 3 or greater hyperthyroidism, withhold KEYTRUDA for severe (Grade 3) hyperthyroidism, and permanently discontinue KEYTRUDA for life-threatening (Grade 4) hyperthyroidism. Isolated hypothyroidism may be managed with replacement therapy without treatment interruption and without corticosteroids.

Other Immune-Mediated Adverse Reactions

Other clinically important immune-mediated adverse reactions can occur. The following clinically significant, immune-mediated adverse reactions occurred in less than 1% of patients treated with KEYTRUDA in Trial 1: exfoliative dermatitis, uveitis, arthritis, myositis, pancreatitis, hemolytic anemia, partial seizures arising in a patient with inflammatory foci in brain parenchyma, Guillain-Barré syndrome, vitiligo, encephalitis, and adrenal insufficiency. Across clinical studies with KEYTRUDA in approximately 2000 patients, the following additional clinically significant, immune-mediated adverse reactions were reported in less than 1% of patients: myasthenic syndrome, optic neuritis, rhabdomyolysis and sarcoidosis in parts of the lymph nodes, skin, or lungs.

For suspected immune-mediated adverse reactions, ensure adequate evaluation to confirm etiology or exclude other causes. Based on the severity of the adverse reaction, withhold KEYTRUDA and administer corticosteroids. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Based on limited data from clinical studies in subjects whose immune-related adverse reactions could not be controlled with corticosteroid use, administration of other systemic immunosuppressants can be considered. Restart KEYTRUDA if the adverse reaction remains at Grade 1 or less. Permanently

discontinue KEYTRUDA for any severe or Grade 3 immune-mediated adverse reaction that recurs and for any life-threatening immune-mediated adverse reaction.

9.1.5 Serious Adverse Reactions Considered Expected for pembrolizumab

SOC	Adverse Reaction (MedDRA Preferred Terms)
Cardiac disorders	Autoimmune myocarditis Myocarditis
Endocrine disorders	Adrenal insufficiency Adrenocortical insufficiency acute Autoimmune thyroiditis Hyperthyroidism Hypophysitis Hypopituitarism Hypothyroidism Lymphocytic hypophysitis Secondary adrenocortical insufficiency Thyroid disorder Thyroiditis
Eye disorders	Autoimmune uveitis Iridocyclitis Iritis Ocular myasthenia Ocular sarcoidosis Uveitis
Gastrointestinal disorders	Autoimmune pancreatitis Colitis Colitis microscopic Diarrhoea Enterocolitis Enterocolitis haemorrhagic Oral lichen planus Pancreatitis Pancreatitis acute Pancreatitis necrotising
General disorders and administration	Pyrexia
Hepatobiliary disorders	Autoimmune hepatitis Drug-induced liver injury Hepatitis Hepatitis acute Hepatitis fulminant

Immune system disorders	Anaphylactic reaction Anaphylactoid reaction Cytokine release syndrome Drug hypersensitivity Hypersensitivity Sarcoidosis Serum sickness
Infections and infestations	Encephalitis Rash pustular
Injury, poisoning and procedural complications	Infusion related reaction
Metabolism and nutritional disorders	Diabetic ketoacidosis Fulminant type 1 diabetes mellitus Latent autoimmune diabetes in adults Type 1 diabetes mellitus
Musculoskeletal and connective tissue disorders	Immune-mediated necrotising myopathy Myopathy Myositis Psoriatic arthropathy Necrotising myositis Polymyositis Rhabdomyolysis
Nervous system disorders	Axonal neuropathy Demyelinating polyneuropathy Diabetic ketoacidotic hyperglycaemic coma Encephalitis autoimmune Guillain-Barre syndrome Limbic encephalitis Miller Fisher syndrome Myasthenia gravis Myasthenia gravis crisis Myasthenic syndrome
Renal and urinary disorders	Autoimmune nephritis Glomerulonephritis Glomerulonephritis membranous Nephritis Nephrotic syndrome Tubulointerstitial nephritis
Respiratory, thoracic and mediastinal disorders	Interstitial lung disease* Pneumonitis* Pulmonary sarcoidosis

Skin and subcutaneous tissue disorders	Acute febrile neutrophilic dermatosis Cutaneous sarcoidosis Dermatitis Dermatitis bullous Dermatitis exfoliative Drug eruption Drug reaction with eosinophilia and systemic symptoms Eczema Erythema multiforme Lichen planus Palmar-plantar erythrodysaesthesia syndrome Pemphigoid Perivascular dermatitis Pruritus Psoriasis Rash Rash erythematous Rash generalised Rash macular Rash maculo-papular Rash morbilliform Rash papular Rash pruritic Skin disorder Skin necrosis Skin toxicity Stasis dermatitis Stevens-Johnson syndrome (SJS)* Subacute cutaneous lupus erythematosus Toxic epidermal necrolysis (TEN)*
For the purpose of safety reporting in clinical trials, only serious adverse reactions are considered expected. *Term also considered expected with fatal outcome.	

9.1.6 Composition

50 mg, lyophilized powder in single-use vial for reconstitution.

9.1.7 Storage Recommendations and Dosage Forms

Two Drug Product (DP) dosage forms are available for MK-3475:a white to off-white lyophilized powder, 50 mg/vial, and a liquid, DP 100 mg/vial, both in Type I glass vials intended for single use only.

- MK-3475 Powder for Solution for Infusion, 50 mg/vial (manufactured using the partially formulated DS), is reconstituted with sterile water for injection prior to use. MK-3475 DP is formulated with L-histidine as buffering agent,

polysorbate 80 as surfactant, sucrose as stabilizer/tonicity modifier, and hydrochloric acid (HCl) and/or sodium hydroxide (NaOH) for pH adjustment (if necessary).

- MK-3475 Solution for Infusion 100 mg/vial is a liquid DP (manufactured using the fully formulated DS with L-histidine as buffering agent, polysorbate 80 as surfactant, and sucrose as stabilizer/tonicity modifier), and has the identical formulation as that of the reconstituted lyophilized vial.

Both drug product dosage forms are stored under refrigerated conditions (2°C - 8°C). The product after reconstitution with sterile water for injection and the liquid drug product are a clear to opalescent solution which may contain proteinaceous and extraneous particulates. The reconstituted lyophilized product and the liquid product are intended for IV administration. The reconstituted DP solution or the liquid DP can be further diluted with normal saline or 5% dextrose in the concentration range of 1 to 10 mg/mL in IV containers made of polyvinyl chloride (PVC) or non-PVC material. Reconstituted vials should be immediately used to prepare the infusion solution in the IV bag and the infusion solution should be immediately administered. If not used immediately, vials and/or IV bags may be stored at 2-8 °C for up to a cumulative time of 20 hours. If refrigerated, the vials and/or IV bags should be allowed to equilibrate to room temperature prior to subsequent use. MK-3475 solutions may be stored at room temperature for a cumulative time of up to 4 hours. This includes room temperature storage of reconstituted or liquid DP solution in vials, room temperature storage of infusion solution in the IV bag and the duration of infusion. This recommendation is based on up to 24 hours of room temperature and up to 24 hours of refrigerated stability data of diluted pembrolizumab solutions in the IV bags.

9.1.8 Dispensation and Accountability

For this study, pembrolizumab (Keytruda®) will be provided by Merck as Pembrolizumab 50 mg (lyophilized powder for injection) or pembrolizumab 100 mg/ 4mL (solution for injection). Please see Appendix J for Preparation and Administration/ Reconstitution of Pembrolizumab (Keytruda®) for Injection (lyophilized powder)

(See also Section 8.3 Treatment Dispensation, Compliance and Accountability for Pembrolizumab)

10.0 **TREATMENT/ DOSE MODIFICATIONS**

10.1 **Unacceptable Toxicity**

Causality for all adverse events should be assessed and if deemed attributable, attempts should be made toward proper attribution.

Drug-related grade 4 toxicities will require subject to discontinue all study treatment. Intolerable grade 2 and grade 3 toxicities should be managed as per dose modification guidelines listed in the table below. Pembrolizumab therapy may be continued providing the residual adverse events are within permissible ranges for pembrolizumab dosing.

10.2 Dose Modification Guidelines for Pembrolizumab

Adverse events (AEs) both serious and non-serious associated with pembrolizumab exposure may represent an immunologic etiology. These AEs may occur shortly after the first dose or several months after the last dose of treatment. Pembrolizumab must be withheld for drug-related toxicities and severe or life-threatening AEs as per Table 10 below. See also Section 8.4 for supportive care guidelines and Appendix I.

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

Table 10.2 Dose Modification and Toxicity Management Guidelines for Immune-related AEs Associated with Pembrolizumab

General instructions:

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

Immune-related AEs	**Toxicity grade or conditions (CTCAEv4.0)**	**Action taken to pembrolizumab**	**irAE management with corticosteroid and/or other therapies**	**Monitor and follow-up**
Steven-Johnson Syndrome (SJS)	Any	Permanently discontinue	Refer patient for specialized care for assessment and treatment.	If SJS confirmed, permanently discontinue pembrolizumab
Toxic Epidermal Necrolysis (TEN)	Any	Permanently discontinue	Refer patient for specialized care for assessment and treatment.	If TEN confirmed, permanently discontinue pembrolizumab
Pneumonitis	Grade 2	Withhold	Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	Monitor participants for signs and symptoms of pneumonitis Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment Add prophylactic antibiotics for opportunistic infections
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold	Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus). • Participants with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV

	Grade 4	Permanently discontinue		infusion.
AST / ALT elevation	3	Withhold	Administer corticosteroids (initial dose of 0.5- 1 mg/kg prednisone or equivalent) followed by taper	Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable
	4	Permanently discontinue --see exception below[2]	Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	
Increased bilirubin	Grade 2	Withhold	Administer corticosteroids (initial dose of 0.5- 1 mg/kg prednisone or equivalent) followed by taper	Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable
	Grade 3 or 4	Permanently discontinue	Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold	Initiate insulin replacement therapy for participants with T1DM Administer anti-hyperglycemic in participants with hyperglycemia	Monitor participants for hyperglycemia or other signs and symptoms of diabetes.
Hypophysitis	Grade 2	Withhold	Administer corticosteroids and initiate hormonal replacements as clinically indicated.	Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue[1]		

Hyperthyroidism	Grade 2	Continue	Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate	Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hypothyroidism	Grade 2-4	Continue	Initiate thyroid replacement hormones (eg, levothyroxine or liothyroinine) per standard of care	Monitor for signs and symptoms of thyroid disorders.
Nephritis and Renal dysfunction	Grade 2	Withhold	Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper.	Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1 or 2	Withhold	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
All other immune-related AEs[3]	Intolerable/ persistent Grade 2	Withhold	Based on type and severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3	Withhold or discontinue based on the type of event. Events that require discontinuation include and not limited to: Gullain-Barre Syndrome, encephalitis		
	Grade 4 or recurrent Grade 3	Permanently discontinue		

1. Withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician.
2. For grade 3 liver toxicity with elevated AST and/or ALT. Since HCC patients may have grade 1-2 elevation of AST/ALT at baseline, if these patients have Grade 3 elevation of AST/ALT, hold therapy and resume treatment when AST/ALT return to baseline or Grade ≤1. The AST/ALT should return to baseline or < 5 x ULN within 12 weeks from start of grade 3, otherwise patient should be discontinued from study.
3. Patients with intolerable or persistent Grade 2 drug-related AE may hold study medication at physician discretion. Permanently discontinue study drug for persistent Grade 2 adverse reactions for which treatment with study drug has been held, that do not recover to Grade 0-1 within 12 weeks of the last dose.

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

10.2.1 Hepatic Toxicity

At baseline, all subjects should be assessed for HBsAg, HBsAb, anti-HBc antibody, HBeAg, and anti-HCV. Patients who test negative for these hepatitis labs do not need to repeat these lab tests again, unless clinically indicated. Evidence of prior HBV should also prompt a viral load measurement at baseline. A viral load <100 IU/mL is required for study entry. Those with active HBV must have been treated with antiviral therapy for ≥3 months before initiation of study treatment. Subjects with controlled HBV on therapy should stay on this therapy throughout pembrolizumab. Subjects who are positive for HBsAg, or anti-HBc (but negative for HBsAg and HBV DNA), should be assessed for viral loads, anti-HBs, anti-HBc and HBsAg every 3 weeks (Q3W), independent of treatment delays.

Viral loads and HBsAg should also be assessed if there is an elevation in ALT >3× baseline, a tenfold or greater increase in HBV or HCV DNA over baseline, or an absolute increase in HBV or HCV DNA over 10^5 c/mL. **If evidence of reactivation is present, the Sponsor should be consulted within 24 hours, and pembrolizumab treatment should be interrupted.**

If there is a 5X or greater elevation in ALT (if normal at baseline), workup should be undertaken to rule out SBP, obstruction, medication, or vascular injury. If these are unrevealing, consideration of pembrolizumab toxicity should be undertaken. Steroids may be considered if viral flare and other etiologies are ruled out.

Table 1: Hepatitis Treatment Guidelines

Test(s)	**Patient Status**	**Included in KN-0224**	**Any HBV Treatment Needed?**
HBsAg (-) Total anti-HBc (+) Anti-HBs (+)	Immune after natural infection	YES	NO
HBsAg (-) Total anti-HBc (-) Anti-HBs (+)	Immune after vaccination	YES	NO
HBsAg (+) Total anti-HBc (+) IgM anti-HBc (+) Anti-HBs (-)	Acute Infection	NO	--
HBsAg (+) Total anti-HBc (+) IgM anti-HBc (-) Anti-HBs (-)	Chronic Infection	YES	YES, need to be on a NI for at for at least 12 week prior to start of Pembro without evidence of a flare

			during that period (ie, has been on chronic NI therapy) EXCLUDE IF: (a) <12 weeks of therapy; (b) HBV DNA not under control during this time frame; (c) Documented HBV flare in the past 12 weeks
HBsAg (-) Total anti-HBc (+) IgM anti-HBc (-) Anti-HBs (-) HBV DNA (negative)	Unclear. Could be: (1) Resolved infection (most common) (2) False positive anti-HBc (so actually NOT HBV infected) (3) Low Level infection (4) Resolving Acute infection	YES	NO
HBsAg (-) Total anti-HBc (+) IgM anti-HBc (-) Anti-HBs (-) HBV DNA (+)	(5) Low Level infection (6) Resolving Acute infection	YES	YES (as above)

11.0 **TREATMENT DISCONTINUATION**

Treatment may be discontinued for any of the following reasons:

- The patient demonstrates progression of disease by RECIST v1.1 (Exception: Patients may remain on the study if in the opinion of the Investigator, he/she is deriving clinical benefit from study treatment)
- The patient withdraws consent from the study
- The patient has not received study treatment for 21 days due to a medical/surgical events or logistical reasons not related to study therapy (e.g. elective surgery, unrelated medical events, patient vacation, and/or holidays).

- The patient experiences an adverse event that in the opinion of the Investigator makes continued study treatment an unacceptable risk
- Intercurrent illness prevents further treatment administration
- The patient has completed 24 months of uninterrupted treatment with pembrolizumab or 35 administrations of study medication, whichever is later. Note: 24 months of study medication is calculated from the date of first dose.
- The patient has confirmed Complete Response (CR) following 24 weeks of pembrolizumab; see Section 8.5.1 for full details
- The patient becomes pregnant (also see Section 15.6 and Appendix A for Expedited Adverse Event Reporting Requirements)
- The patient requires continuous treatment with a prohibited concomitant drug(s) for which no safe alternatives can be substituted
- The patient is significantly noncompliant with the requirements of the protocol

Should discontinuation of study therapy occur, all efforts should be made to execute/ report End-of-Treatment and Follow-up Evaluations as completely as possible and to determine/ document the reason for discontinuation (unless the patient withdraws consent for follow-up).

If a patient wishes to withdraw consent from the study, the PI must be notified. The information regarding withdrawal (i.e. subject identifiers and date of withdrawal) should be documented in the subject's record and updated within any other research database(s).

12.0 SCHEDULE OF CLINICAL & LABORATORY EVALUATIONS

Prior to performing any study-specific procedures or evaluations, written informed consent and authorization for the use of protected health information (HIPAA) must be obtained in accordance with all applicable policies, regulations and laws.

Correlative evaluations (optional) will also be performed at specified visits. Please refer to Section 1.5 and 13.0 CORRELATIVE STUDIES for details.

Imaging studies should be done *every 3 cycles (every 9 weeks, ±9 days)* from the date of Enrollment timed to coincide with the end of the prior treatment cycle; assessing all known sites of disease using the same type(s) of scan(s) that was/were performed at baseline.

All evaluations should be completed as detailed below, prior to the administration of trial treatment on Day 1 of each cycle. All evaluations will be administered on an outpatient basis.

12.1 Pre-Treatment Evaluations (Screening)

The following must be collected/ performed within 28 days prior to Cycle 1, day 1 of treatment. Clinical and laboratory evaluations performed as part of routine standard of care do not need to be repeated if performed within the appropriate window.

- Complete medical history, disease history and prior medical treatments
- Demographic data (age, gender, and race)
- Height
- Weight
- Vital signs (V/S)
    - Oral temperature
    - Blood pressure
    - Heart rate
- Complete physical examination (PE)
- ECOG Performance Status (PS)
- 12-Lead Electrocardiogram (ECG)
- Urine or serum pregnancy test for women of child-bearing potential (WoCBP)
- Complete Blood Count (CBC) with differential (diff)
- Coagulation studies:
    - PT/INR,
    - aPTT
- Comprehensive Serum Chemistry Panel (see Section 10.2.1 for hepatic toxicity guidelines)
    - Albumin,
    - Alkaline phosphatase (alk phos),
    - Total bilirubin,
    - Calcium (Ca),
    - Chloride (Cl),
    - Creatinine,
    - Potassium (K),
    - Total Protein,
    - SGOT (AST),
    - SGPT (ALT),
    - Sodium (Na),
    - Blood urea nitrogen (BUN),
    - Liver function tests (LFTs),
- Thyroid Tests
    - T3
    - T4
    - TSH
- Alpha-fetoprotein (AFP)
- Lipase,
- Amylase and,
- Hepatitis B Virus (HBV) Testing (see Section 10.2.1 for hepatic toxicity guidelines)

- HBsAg,
- HBsAb,
- anti-HBc antibody,
- HBeAg

- Hepatitis C Virus (HCV) Testing (see Section 10.2.1 for hepatic toxicity guidelines)
  - anti-HCV
- Urinalysis (U/A)
- Correlative Studies (See Section 1.5 and 13.0)
- Imaging Studies: Imaging studies for tumor assessment for all known sites of disease, (including triple phase CT or MRI of abdomen with contrast)
- Baseline symptoms

12.2 Evaluations on Treatment

Collection of Concomitant Medications and Adverse Events (AEs) should occur throughout the study, as described. Any SAE, or follow up to a SAE, 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 end of treatment, or the initiation of new anti-cancer therapy, whichever is earlier, whether or not related to the Merck product, must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety. All subjects with SAEs must be followed up for outcome. (See Section 15.0 and Appendix A for details).

12.2.1 Day 1 (±3 days, unless otherwise specified), all Cycles: Trial Treatment Administration

- Medical History
- Complete PE
- ECOG PS
- V/S
  - Oral temperature
  - Blood pressure
  - Heart rate
- Weight
- CBC with diff
- Comprehensive Serum Chemistry Panel (see Section 10.2.1 for hepatic toxicity guidelines)
  - Albumin,
  - Alkaline phosphatase (alk phos),
  - Total bilirubin,
  - Calcium (Ca),
  - Chloride (Cl),
  - Creatinine,

  - Potassium (K),
  - Total Protein,
  - SGOT (AST),
  - SGPT (ALT),
  - Sodium (Na),
  - Blood urea nitrogen (BUN),
  - Liver function tests (LFTs),
- Alpha-fetoprotein (AFP)
- Lipase and amylase, only if clinically indicated
- Thyroid Tests
  - T3
  - T4
  - TSH
- HBV/ HCV Testing (if tested positive at screening)
  - See Section 10.2.1 for hepatic toxicity guidelines
- Correlative Studies (Optional, See Section 1.5 and 13.0)
- *(Imaging studies for tumor assessment for all known sites of disease (including CT or MRI of abdomen with contrast): the same method of assessment and technique used at baseline will be used during treatment and follow-up. Imaging studies will be done every 3 cycles (**after every 9 weeks, ±9 days**) from the date of Enrollment, timed to coincide with the end of the prior treatment cycle.)*

12.3 **Off-Treatment Evaluations**

The following assessments must be performed at the Off-Treatment visit (±5 days).

- Medical History
- Complete PE
- V/S
- Weight
- ECOG PS
- CBC with diff
- Comprehensive Serum Chemistry Panel
  - Albumin,
  - Alkaline phosphatase (alk phos),
  - Total bilirubin,
  - Calcium (Ca),
  - Chloride (Cl),
  - Creatinine,
  - Potassium (K),
  - Total Protein,
  - SGOT (AST),
  - SGPT (ALT),

  - Sodium (Na),
  - Blood urea nitrogen (BUN),
  - Liver function tests (LFTs),
- Alpha-fetoprotein (AFP)
- Lipase and amylase, only if clinically indicated
- Thyroid Tests
  - T3
  - T4
  - TSH
- Correlative Studies (Optional, See Section 1.5 and 13.0)
- *Imaging studies for tumor assessment for all known sites of disease (including CT or MRI of abdomen with contrast): the same method of assessment and technique used at baseline will be used during treatment and follow-up.*

12.4 **30 Days After Off Treatment (OT) Safety Evaluations**

The following safety assessments must be performed at 30-days (+ 5 days) after Off Treatment date.

- Coagulation studies:
  - PT/INR,
  - aPTT
- Comprehensive Serum Chemistry Panel
  - Albumin,
  - Alkaline phosphatase (alk phos),
  - Total bilirubin,
  - Calcium (Ca),
  - Chloride (Cl),
  - Creatinine,
  - Potassium (K),
  - Total Protein,
  - SGOT (AST),
  - SGPT (ALT),
  - Sodium (Na),
  - Blood urea nitrogen (BUN),
  - Liver function tests (LFTs),
- Alpha-fetoprotein (AFP)
- Lipase and amylase, only if clinically indicated
- Thyroid Tests
  - T3
  - T4
  - TSH
- Correlative Studies (Optional, See Section 1.5 and 13.0)

- *(Any SAE, or follow up to a SAE, 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 end of treatment, whether or not related to the Merck product, must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety. All subjects with SAEs must be followed up for outcome. (See Section 15.0 and Appendix A for details).)*

12.5 **Follow-up Evaluations**

For patients without documented evidence of objective disease progression the following assessments should be performed every 12 weeks until documented disease progression, death, withdrawal of consent, or end of study, whichever occurs first. A *telephone call* to the patient and/or the patient's family may be made to evaluate the patient's status on the following:

- Post-study anticancer therapy status
- Survival status
- Following confirmed disease progression or initiation of new anti-cancer therapy, survival will be assessed (at a minimum) by telephone contact every 12 weeks (±2 weeks)."

12.6 Calendar of Clinical and Laboratory Evaluations

	Screening	**Treatment Cycle(s)** q21 days	**Off Treatment** ±5 days	**Safety Evaluation**	**Follow-Up**
	≤28 days prior [A]	Day 1 (±3 days unless specified)		30-days (+5 days) after Off Treatment	every 12 weeks [K]
ICF	X				
Eligibility	X				
Demographics [B]	X				
Complete Medical History [C]	X	X	X		
Height	X				
Weight	X	X	X	X	
Vital Signs [D]	X	X	X	X	
Complete PE	X	X	X	X	
ECOG PS	X	X	X	X	
12-Lead ECG	X				
CBC with diff	X	X	X	X	
Comp Serum Chemistry Panel [E]	X	X	X	X	
Alpha-fetoprotein (AFP)	X	X	X	X	
Lipase & Amylase	X	(X, repeat only if clinically indicated)			
T3, T4 and TSH	X	X	X	X	
PT/INR, aPTT	X			X	
HBV and HCV Testing	X (Section 12.1)	X (Section 10.2.1)			
Urine or serum pregnancy test [F]	X				
Urinalysis	X				
Correlative Studies: Tissue Sample [G] (Archival or newly obtained)	X				
Correlative Studies: Peripheral Blood [H] (Serum)	X	X [H]	X [H]	X [H]	
Imaging studies [I]	X	(X)	X		
Pembrolizumab IV administration		X			
Baseline Symptoms	X				
Adverse Events		X			(X) [J]
Concomitant Medications	X				
Telephone Call [L]					X

[A] Screening evaluations should be done within 28-days prior unless otherwise specified.

[B] Demographic data includes age, gender and racial/ethnic background.

[C] Complete Medical History includes disease history and prior medical treatments.

[D] Vital signs include oral temperature, blood pressure and heart rate.

[E] Comprehensive Serum Chemistry Panel includes albumin, alkaline phosphatase, total bilirubin, sodium, calcium, chloride, creatinine, potassium, total protein, AST (SGOT), ALT (SGPT), blood urea nitrogen,.

[F] Urine or serum (beta-HCG) pregnancy test is required for women of childbearing potential **within 3-days prior to Day 1** of trial treatment.

[G] Tissue sample (either archival or newly obtained) is optional and for correlative studies (see Section 1.5 and 13.0 for details).

[H] Serum collection for correlative studies is optional (see Section 1.5 and 13.0 for details). Samples will be collected at baseline, during treatment and/or at the time of documented disease progression, whichever occurs first.

[I] Imaging studies for tumor assessment for all known sites of disease (including CT or MRI of abdomen with contrast): the same method of assessment and technique used at baseline will be used during treatment and follow-up. Imaging studies will be done every 3 cycles (**after every 9 weeks, ±9 days**) from the date of Enrollment, timed to coincide with the end of the prior treatment cycle.)

[J] AE/SAE collections should continue for at least 90-days post EoT visit. All subjects with SAEs must be followed up for outcome. (See Section 15.0 and Appendix A for details).

[K] Follow-up for patients without documented objective disease progression shall occur every 12 weeks (+/- 2 weeks) until documented disease progression, death, withdrawal of consent, or EoS, whichever occurs first.

[L] Telephone call may be made to patient or patient's family to follow-up on patients' post-study anticancer therapy and survival status. Following confirmed disease progression or initiation of new anti-cancer therapy, survival will be assessed (at a minimum) by telephone contact every 12 weeks (±2 weeks).

13.0 SCHEDULE OF CORRELATIVE EVALUATIONS

The following optional samples may be collected (at the discretion of the PI) at the specified time points if the patient consents to them:

13.1 Pre-Treatment Specimen Collection (Screening)

- Tissue sample (archival **or** newly obtained)
- Approximately up to 30 mL peripheral blood (2 green top tubes + 1 red top tube + 1 EDTA tube)

13.2 On Treatment Specimen Collection

13.2.1 Every 12 weeks (3 months), all Cycles: Trial Treatment Administration

- Approximately up to 30 mL peripheral blood (serum for biomarkers)

13.2.2 At Week 9 **and** Week 18: Trial Treatment Administration

- Approximately up to 30 mL peripheral blood

13.3 Off-Treatment Specimen Collection (or at time of documented disease progression)

The following must be performed at the Off-Treatment visit (±5 days):

- Approximately up to 30 mL peripheral blood (serum for biomarkers)
- Additional 7 mL peripheral blood, *only* if prior to Week 9 or Week 18

13.4 30 Days after Off Treatment Safety visit

The following must be performed at the EOT safety visit and should occur 30-days (+5 days) after the last dose of study treatment.

- Approximately up to 30 mL peripheral blood (serum for biomarkers)

13.5 Calendar of Specimen Collection for Correlative Studies

Timepoints	Tissue Sample	Peripheral Blood
Screening	X	X (Up to 30 mL)
Week 9		X (Up to 30 mL)
Every 12 weeks (3 months), all Cycles		X (Up to 30 mL)
Week 18		X (Up to 30 mL)
Off Treatment (or at time of documented disease progression)		X (Up to 30 mL) (plus additional 7mL, *only* if prior to Week 9 or 18)
30 Days after Off Treatment Safety Visit		X (Up to 30 mL)

14.0 MEASUREMENT OF EFFECT

14.1 Antitumor Effect in Solid Tumors

For the purposes of this study, patients should be re-evaluated for response every 9 weeks (± 9 days) which corresponds to the 3 week cycles of therapy. In addition to a baseline scan, confirmatory scans should also be obtained ≥4 weeks following initial documentation of objective response. *(Note*: Lesions are either measurable or non-measurable using the criteria provided below. The term "evaluable" *in reference to measurability* will not be used because it does not provide additional meaning or accuracy.)

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

The following general principles must be followed:
1. To assess objective response, it is necessary to estimate the overall tumor burden at baseline to which subsequent measurements will be compared. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than four weeks before registration.

2. Measurable disease is defined by the presence of at least one measurable lesion.

3. All measurements should be recorded in metric notation by use of a ruler or calipers.

4. The same method of assessment and the same technique must be used to characterize each identified lesion at baseline and during follow-up.

14.2 Definitions

Evaluable for Objective Response

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

Evaluable Non-Target Disease Response

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

14.3 Disease Parameters

Measurable Disease

Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm by chest x-ray, as ≥ 10 mm with CT scan, or ≥ 10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters.

NOTE: Tumor lesions that are situated in a previously irradiated area may be considered measurable if they have grown subsequent to previous radiation.

Malignant Lymph Nodes

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

Non-measurable Disease

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

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

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

Target Lesions

All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured

reproducibly should be selected.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum of the diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target Lesions

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

14.4 Methods for Evaluation of Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks (28 days) before the beginning of treatment.

The same method of assessment and the same technique must be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical Lesions

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

Chest X-ray

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

Conventional CT and MRI

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

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal

resolution; however, there are many image acquisition variables involved in MRI which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up must be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

Ultrasound

Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy

The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Tumor markers

Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published [JNCI 96:487-488, 2004; J Clin Oncol 17, 3461-3467, 1999; J Clin Oncol 26:1148-1159, 2008]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer [JNCI 92:1534-1535, 2000].

Cytology, Histology

These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or

stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

14.5 Response Criteria

14.5.1 Evaluation of Target Lesions

Complete Response (CR)
Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.

Partial Response (PR)
At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters

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

Stable Disease (SD)
Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

14.5.2 Evaluation of Non-Target Lesions

Complete Response (CR)
Disappearance of all non-target lesions. All lymph nodes must be non-pathological in size (<10 mm short axis). Note: If tumor markers are initially above the ULN, they must normalize for a patient to be considered in complete CR.

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

Progressive Disease (PD)
Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

When the patient also has measurable disease, there must be an overall level of substantial worsening in non-target disease such that, even in the presence of SD or PR

in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest "increase" in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the patient only has non-measurable disease, the increase in overall disease burden should be comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e., an increase in tumor burden from "trace" to "large", an increase in nodal disease from "localized" to "widespread", or an increase sufficient to require a change in therapy.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

14.5.3 Evaluation of New Lesions

The appearance of new lesions constitutes Progressive Disease (PD).

A growing lymph node that did not meet the criteria for reporting as a measurable or non-measurable lymph node at baseline should only be reported as a new lesion (and therefore progressive disease) if it:

a) increases in size to ≥15 mm in the short axis or;

b) there is new pathological confirmation that it is disease (regardless of size).

14.5.4 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence or non-protocol therapy (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of measurement criteria.

Target Lesions	**Non-Target Lesions**	**New Lesions***	**Best Overall Response**	**Remarks**
CR	CR	No	CR	Confirm by repeat assessments ≥4 weeks after criteria for response are first met.
CR	Non-CR/Non-PD***	No	PR	
CR	Not evaluated	No	PR	
PR	Non-PD***/not evaluated	No	PR	

SD	Non-PD***/not evaluated	No	SD	Follow-up assessments must have met SD criteria at least once ≥8 weeks from study entry.
PD	Any	Yes or No	PD	No prior SD, PR or CR
Any	PD**	Yes or No	PD***	
Any	Any	Yes	PD	

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

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

*** PD in non-target lesions should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase. Please refer to the Evaluation of Non-Target Lesions – Progressive Disease section for further explanation.

- **Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration.*"** Every effort should be made to document the objective progression even after discontinuation of treatment.
- In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of CR depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before confirming the CR status.

14.5.5 Duration of Response

Duration of Overall Response

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

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

Duration of Stable Disease

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

14.6 Disease Control Rate (DCR)

DCR is the proportion of patients whose best overall response per RECIST criteria is complete response (CR), partial response (PR), or stable disease (SD). Disease control must be confirmed by repeat assessments performed at an interval of no less than 4 weeks for CR and PR. For SD, disease control must be confirmed by repeat assessments performed at an interval of no less than 8 weeks.

14.7 Overall Response Rate (ORR)

ORR is the proportion of patients whose best overall response per RECIST criteria is complete response (CR) or partial response (PR).

14.8 Progression-Free Survival (PFS)

PFS is defined as the elapsed time from the date of first study treatment to the earliest date of documented disease progression or death from any cause, whichever is earlier. For patients who remain alive without progression, follow up time will be censored at the date of last disease assessment.

14.9 Overall Survival (OS)

OS is defined as the elapsed time from start of treatment to death or date of censoring. Patients alive or those lost to follow-up will be censored at the last date of contact (or last date known to be alive).

15.0 ADVERSE EVENTS

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 will be utilized for adverse event reporting.

15.1 Purpose

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies, as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. Additionally, certain adverse events must be reported in an expedited manner for timelier monitoring of patient safety and care.

15.2 Adverse Event

Adverse Event (AE): Can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, medical treatment, or procedure without judgment about causality. An adverse event can arise from any use and from any route of administration, formulation, or dose including an overdose. This includes any newly occurring event or a previous condition that has increased in severity or frequency since initiation of a drug, medical treatment, or procedure.

Abnormal Findings

In any clinical assessment, a value outside the normal or reference range (such as a clinical laboratory, vital sign, or ECG) will not be reported or assessed as an AE unless that value is considered to be of clinical significance by the investigator. A value of clinical significance is one that leads to discontinuation or delay in protocol treatment, dose modification, therapeutic intervention*, or is considered to be a clinically significant new finding or change from baseline by the investigator.

*Transfusion support administered to offset clinical symptoms of anemia or thrombocytopenia will not be considered therapeutic intervention.

Signs and Symptoms
Signs/symptoms resulting from an underlying clinical diagnosis should be documented as one comprehensive AE. If no underlying clinical diagnosis can be identified, each sign/symptom should be reported as a separate independent event. (A new or worsening event resulting from an underlying clinical diagnosis or a reaction to concurrent medications should be documented as a separate independent AE unless it is within the normal range of fluctuation for that patient.)

Grade Changes/Fluctuations
AEs will be reported at the maximum grade/severity experienced for the duration of the event. Should one particular event warrant further investigation, additional details may be collected at the discretion of the Principal Investigator.

Progression of Disease
Progression of disease, if documented in accordance to standard of care, should not be reported as an AE.

Tests and Procedures
Tests and procedures should not be reported as AEs. The underlying clinical diagnosis (or sign/symptom in the event an underlying clinical diagnosis is not known) requiring testing or a procedure, should be reported as an adverse event if it meets criteria for reporting.

15.3 Serious Adverse Events (see also Appendix A)

Serious AE (SAE) means any untoward medical occurrence that occurs at any dose:

1. **Results in death.**
2. **Is life-threatening.**
   The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe).
3. **Requires inpatient hospitalization or prolongation of present hospitalization.**
   Elective hospitalization to simplify protocol treatment/evaluations or to treat a baseline condition that did not worsen from baseline will not be considered an SAE.
4. **Results in persistent or significant disability/incapacity.**
   Disability is defined as a substantial disruption of a person's ability to conduct normal life functions.
5. **Is a congenital anomaly/birth defect**.
6. **Is a medically important event.**
   A medically important event may not be immediately life threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to

prevent one of the other outcomes listed in the definition above, or involves suspected transmission via a medicinal product of an infectious agent. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse; any organism, virus, or infectious particle (e.g., prion protein transmitting Transmissible Spongiform Encephalopathy), pathogenic or nonpathogenic, is considered an infectious agent.

Additional SAE classification(s) for AEs occurring at any dose or during any use of Merck product(s):

1. **Is a new cancer (that is not a condition of the study);**
2. **Is associated with 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.

15.4 Adverse Event Collection Period

In this protocol, adverse events include only treatment-emergent adverse events. A treatment-emergent adverse event (TEAE) is defined as any event that begins or worsens after the start of protocol treatment. All baseline-emergent adverse events, any event that begins or worsens after completion of the informed consent but prior to the start of protocol treatment, should be reported as a Baseline/Comorbid Condition.

All adverse events that occur within ≤ 30 days of the last dose of study therapy will be reported and followed until resolution. Resolution is defined as a return to baseline status or the stabilization of an event with the expectation that it will remain chronic. (Exception: If a patient begins an alternative therapy that confounds accurate assessment of AEs within ≤ 30 days of the last dose of study therapy, all adverse event collection will stop and any ongoing events will be left open.)

15.5 Adverse Event Reporting Requirements

The information to be reported in AEs will be assessed by and assigned severity using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 4.03. The NCI CTCAE provides descriptive terminology and a grading scale for each adverse event listed. A copy of the NCI CTCAE v4.03 can be downloaded from the CTEP home page (http://evs.nci.nih.gov/ftp1/CTCAE/About.html).

Information to be reported in the description of each adverse event may be included, but is not limited to:

1. Clinical Diagnosis of the event as determined by NCI CTCAE, Version 4.03 descriptive terminology. If no clinical diagnosis can be identified, each sign/symptom should be reported as a separate independent event.
2. Date of onset of the AE (start date).
3. Date of resolution of the AE (end date).
4. Severity of the event determined by NCI CTCAE, Version 4.0 grading scale.
5. Relationship of the AE to study therapy. Categorized as follows:

Definite	The adverse event is clearly related to the investigational agent(s)
Probable	The adverse event is likely related to the investigational agent(s)
Possible	The adverse event may be related to the investigational agent(s)
Unlikely	The adverse event is doubtfully related to the investigational agent(s)
Unrelated	The adverse event is clearly not related to the investigational agent(s)

6. Whether or not the AE is Serious or Not Serious as defined in Section 15.3 Serious Adverse Events.
7. Whether the AE is Suspected and/or Unexpected.

Suspected	Any AE for which there is a reasonable possibility that the drug caused the AE. For the purposes of expedited safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the AE.
Unexpected	Any AE for which the nature or severity of the event is not consistent with the applicable product information, e.g., the Investigator's Brochure or Package Insert.

8. Action taken as a result of the AE.
9. Outcome.

15.6 Expedited Adverse Event Reporting Requirements

All AEs, regardless if serious or not, will be described in the source documents, reported on the applicable AE page of the CRFs, and entered into *Velos*. However, certain adverse events must also be reported in an expedited manner for more timely monitoring of patient safety and care. Appendix A provides information about these expedited reporting requirements.

16.0 STATISTICAL CONSIDERATIONS

16.1 Objectives and Endpoints

This is a single-arm phase II trial of Pembrolizumab (Keytruda®) in patients with advanced, unresectable hepatocellular carcinoma. The primary objective is to assess its therapeutic efficacy in patients with unresectable hepatocellular carcinoma (HCC). The

primary endpoint is disease-control rate (DCR) defined as the proportion of patients achieving a best overall response of either a CR, PR or SD (that is maintained for at least 8 weeks).

Secondary endpoints include progression-free survival (PFS), overall survival (OS), objective response rate (ORR), duration of response (DOR), and toxicity profile of Pembrolizumab. We will also evaluate the expression levels of PD-L-1 in tumor tissue, as well as serum titers of hepatitis B or C in patients with hepatitis B or C, respectively, for whom specimens are available.

16.2 Study Design and Sample Size Justification

The primary endpoint for this single arm phase II trial is disease control rate (CR, PR, or SD). The rationale for using disease control rate (DCR) as the primary endpoint is derived from the clinical experience with Sorafenib (SHARP trial 2008), which was approved as the first and only therapeutic agent definitively proven to prolong survival in patients with advanced HCC. The disease control rate of Sorafenib was 43% in the SHARP trial [7]. We hypothesize that Pembrolizumab will achieve a similar or higher disease control rate. We set a null hypothesis rate of 18% disease control, since standard chemotherapy regimens generally result in a DCR of 15-20%.

We propose study size based on the Simon 2-stage MiniMax design [39] with a one-sided significance level of 5% and 90% power. Assuming that Pembrolizumab therapy will not be of further interest if DCR were no better than 18% (null hypothesis) while a rate of 43% would merit further investigation, the Simon MiniMax design requires at most 28 patients: 14 patients to be enrolled in the first stage and possibly an additional 14 in the second stage. If no more than 2 of the 14 patients in stage 1 achieve CR/PR/SD, the trial will stop and Pembrolizumab will be considered ineffective. If 3 or more of the stage 1 patients achieve CR/PR/SD, our study will continue to a second stage and enroll an additional 14 patients for a total of 28. If 9 or more out of 28 study patients achieve CR/PR/SD, we will report an observed DCR of at least 32% and conclude that the true DCR significantly exceeds a null rate of 18%. With this design, the chance of early stopping at the end of stage 1 is 53% if the null hypothesis of 18% DCR is true, whereas there is a very small chance, 2%, of early termination if the true DCR is 43%.

16.3 Analysis Set

Patients who are study eligible and receive at least one dose of Pembrolizumab will be considered evaluable for efficacy and toxicity, and will comprise the main analysis set.

Any patient who is enrolled on study but does not receive study treatment will be excluded from all analyses. Any patient who receives study treatment but is later found to be ineligible (e.g. protocol violation) will be withdrawn from study but will be followed for response, toxicity, and survival. The experience of such patients will be characterized separately from that of evaluable patients. Reasons for all exclusions will be characterized, such as eligibility subsequently not confirmed, or failure to receive treatment.

16.4 Patient Enrollment and Study Duration

We plan to enroll up to 35 patients, to ensure that we have a minimum of 28 patients who are evaluable for the primary efficacy endpoint for this study, disease control rate (DCR). We expect to enroll 10-12 patients per year based on our institution's enrollment capacity.

Accrual will be suspended after 14 evaluable patients (stage 1) in order to assess DCR in accordance with the two-stage design of this trial.

16.5 Statistical Analysis

Demographics and baseline disease and treatment characteristics will be summarized using descriptive statistics such as counts and percentages, mean, standard deviation, median and range, as appropriate. This will include age, sex, race/ethnicity, performance status, prior systemic therapy, laboratory parameters (bone marrow function, liver function, etc.), and disease characteristics such as site (visceral, non-visceral), Child-Pugh classification and stage.

The number of Pembrolizumab injections received and reasons for treatment discontinuation will be summarized descriptively. Safety data, including toxicities, reasons for withdrawal from study treatment and laboratory data will also be summarized descriptively. Toxicities will be tabulated by type, grade, duration and attribution to treatment. A patient-level summary by worst grade toxicity will be included.

Efficacy analysis will include the primary study endpoint disease control rate (DCR), as well as the secondary endpoints, which include objective response rate (CR+PR), progression-free survival and overall survival. Disease control rate and overall response rate will be estimated by the percentage of patients achieving these criteria and the corresponding 95% confidence interval using the exact binomial method [40].

In addition, we will report median and range for the time to onset and duration of response for patients who achieve CR or PR. For patients whose best response is SD, we will report the median and range of SD duration.

The Kaplan-Meier method will be used to estimate progression-free and overall survival rates and corresponding median times, if attained. Point estimates with corresponding 95% confidence intervals based on Greenwood's variance and the log-log transform method will be given for the proportion of progression-free/surviving patients at selected times, such as 3, 6, 12, 18, and 24 months following the initiation of treatment, as well as for median times, if attained [41]. For purposes of these analyses, progression-free survival will be measured from start date of treatment to date of documented disease progression, or death from any cause, whichever occurs first. Patients who are alive and progression-free will be censored at their date of last documented progression-free status. Overall survival will be measured from start date of treatment to date of death from any cause. Patients who are alive will be censored at their date of last contact. To the extent possible with 28 patients, we will explore the effect of baseline characteristics on progression-free and overall survival using Cox regression [42]. The objective response rate (ORR) will be estimated by the percentage of patients and corresponding 95% confidence interval using the exact binomial method.

To the extent that biomarker data are available, we will summarize expression levels of PD-L- 1 in tumor tissue, and serum titers of hepatitis B and/ hepatitis C in patients with hepatitis B or C, respectively, using descriptive statistics. A descriptive analysis will be done for hypothesis-generating purposes but a statistical analysis will not be done as there may not be enough tumor tissue and blood samples collected (to conduct a formal statistical analysis).

17.0 DATA REPORTING

Data must be submitted according to the protocol requirements for all patients registered. Patients for whom documentation is inadequate to determine eligibility will generally be deemed ineligible.

17.1 Data and Safety Monitoring

The Sylvester Comprehensive Cancer Center (SCCC) Data and Safety Monitoring Committee (DSMC) will monitor this clinical trial according to the Cancer Center's DSM Plan. In its oversight capacity, the DSMC bears responsibility for suspending or terminating this study. DSMC oversight of the conduct of this trial includes ongoing review of accrual and adverse event (AE) data, and periodic review of the study therapy. The guidelines appearing in this section are offered for DSMC consideration in assessing AEs and response to study treatment. In addition, the DSMC will review reports from all audits, site visits, or study reviews pertaining to this clinical trial and take appropriate action. The SCCC DSM Plan to which this study is subject can also be found at www.sylvester.org.

17.2 Stopping Rules (for the study as a whole)

17.2.1 Early Stopping Guidelines

We propose the following guidelines for the DSMC in its review of accumulating data. For safety, we propose early stopping guidelines based on a Bayesian method. Early stopping guidelines for lack of efficacy are built into the Simon 2-stage design for this trial. Specific details are presented in the remainder of this section.

17.2.2 Safety: Early Stopping Due to Excessive Toxicity

We propose the following guidelines for the DSMC in its review of accumulating data on toxicity. The proposed guidelines were developed using Bayesian methods, which can be applied at any stage of enrollment without advance specification of the number of interim analyses to be performed, or the number of patients evaluable for toxicity, at the time such assessments are made [43-44].

Under the Bayesian method, we assign a prior probability (level of belief at the start of the trial) to a range of possible values for the true toxicity rate. As data on treated patients become available, each of these probability distributions is revised

and the resulting posterior probability becomes the basis for recommending either early termination or continuation of the study. Specific stopping guidelines and details on the prior distribution assumptions, and the resulting posterior probabilities are presented below.

For purposes of safety monitoring, we define an unacceptable toxicity to be any treatment-related (i.e., possible, probable, or definite) grade 3 or higher toxicity excepting nausea, reversible elevation of liver function tests and reversible myelosuppression. Prolonged (defined as ≥12 weeks,) grade 3 or higher elevation of liver function tests or myelosuppression will be considered unacceptable. Patients with hepatitis may take longer to recover their counts but it is considered justifiable given their poor prognosis. Early stopping (suspension and possibly termination) will be considered if there is evidence that the proportion of patients experiencing unacceptable toxicity exceeds 20%.

Specifically, we suggest as a guideline for early termination, a posterior probability of 90% or higher that the rate of unacceptable toxicity exceeds 20%. The table below shows specific instances where this guideline is met, thus suggesting early termination due to evidence of excessive toxicity.

For example, if 8 evaluable patients have been assessed for toxicity, the second row of the above table indicates that early stopping should be considered if 4 (or more) of these patients have experienced unacceptable toxicity. Note that 4 of 8 patients with unacceptable toxicity is an observed toxicity rate of 50%.

Posterior probabilities used to derive the preceding table are calculated under a prior beta distribution with parameters $\beta_1 = 0.4$ and $\beta_2 = 1.6$, which corresponds to an expected rate of 20% based on very limited information, roughly equivalent to having studied two patients. This prior distribution implies an a priori chance of 36% that the rate of unacceptable toxicity is 20% or greater.

Number of patients with unacceptable toxicity*	Total patients evaluated	Observed toxicity rate
3	4 to 6	≥ 50%
4	7 to 10	≥ 40%
5	11 to 13	≥ 39%
6	14 to 17	≥ 35%
7	18 to 21	≥ 33%
8	22 to 25	≥ 32%
9	26 to 27	≥ 32%

*Possibly, probably or definitely treatment-related, grade 3+ toxicity excepting nausea, reversible elevation of liver function tests and reversible myelosuppression.

17.2.3 Early Stopping for Lack of Efficacy

The Simon two-stage design of this trial, described in Section 16.2, provides for a single interim analysis of the primary study endpoint, disease control rate (DCR).

After enrollment of the first 14 evaluable patients in stage 1, accrual will be suspended and a decision to terminate the study early or continue accrual will be made. DCR of this cohort of 14 evaluable patients from stage 1 will be determined as a best overall response of either a CR, PR, or SD (as detailed in section 14.5). If no more than 2 of the first 14 patients achieve DCR, the trial will stop and pembrolizumab will be considered ineffective, as this suggests that the DCR is no better than the null hypothesis rate of 18%. If DCR is achieved in 3 or more of the first 14 patients, the trial will continue to a second stage and enroll an additional 14 patients for a total evaluable number of 28 patients. The findings of interim analysis of DCR from the first 14 patients of stage 1 will be reported to the Sylvester DSMC.

17.2.4 No Early Stopping for Treatment Efficacy

We do not intend to stop the study early if the proposed study treatment appears to be effective. Under such circumstance, continuation of the trial will yield additional information regarding the magnitude of the true DCR. Moreover, if results from this study are promising, further studies will be needed to fully assess the benefits and risks of Pembrolizumab therapy in the treatment of patients with advanced unresectable hepatocellular carcinoma.

18.0 STUDY AUDITING AND MONITORING

This study will be audited and monitored according to http://uresearch.miami.edu/regulatory-compliance-services/rcqa and the Office of Research Integrity Assurance, respectively.

19.0 INVESTIGATOR RESPONSIBILITIES

19.1 Investigator Responsibility/Performance

The investigator will ensure that this study is conducted in accordance with all regulations governing the protection of human subjects. The investigator will ensure that all work and services described in or associated with this protocol will be conducted in accordance with the investigational plan, applicable regulations, and the highest standards of medical and clinical research practice.

19.2 Confidentiality

The investigator must ensure that each subject's anonymity will be maintained and each subject's identity will be protected from unauthorized parties. A number will be assigned to each subject upon study entry and the number and the subject's initials will be used to identify the subject for the duration of the study. The investigator will maintain all documents related to this study in strict confidence.

19.3 Informed Consent and Permission to Use Protected Health Information

It is the responsibility of the investigator to obtain written informed consent from each subject participating in this study after adequate explanation, in lay language, of the methods, objectives, anticipated benefits, and potential hazards of the study. The investigator must also explain that the subject is completely free to refuse to enter the study or to discontinue participation at any time (for any reason) and receive alternative conventional therapy as indicated. Prior to study participation, each subject will sign an IRB approved informed consent form and receive a copy of same (and information leaflet, if appropriate). For subjects not qualified or able to give legal consent, consent must be obtained from a parent, legal guardian, or custodian. The investigator or designee **must** explain to the subject before enrollment into the study that for evaluation of study results, the subject's protected health information obtained during the study may be shared with the study sponsor, regulatory agencies, and the IRB. It is the investigator's (or designee's) responsibility to obtain permission to use protected health information per HIPAA from each subject, or if appropriate, the subjects' parent or legal guardian.

19.4 Source Documentation and Investigator Files

The investigator must maintain adequate and accurate records to fully document the conduct of the study and to ensure that study data can be subsequently verified. These documents should be classified into two separate categories: (1) investigator study file and (2) subject clinical source documents that corroborate data collected on the CRF's. Subject clinical source documents may include hospital/clinic patient records; physician's and nurse's notes; appointment book; original laboratory, ECG, EEG, radiology, pathology, and special assessment reports; pharmacy dispensing records; subject diaries; signed informed consent forms; and consultant letters. When the CRF or any form is used as the source document, this must be clearly stated in the investigator study file. Minimally, the following be documented in source documents:

- Medical history/physical condition and diagnosis of the subject before involvement in the study sufficient to verify protocol entry criteria
- Study number, assigned subject number, and verification that written informed consent was obtained (each recorded in dated and signed notes on the day of entry into the study)
- Progress notes for each subject visit
- Documentation of treatment
- Laboratory test results
- Adverse events (action taken and resolution)
- Condition and response of subject upon completion of or early termination from the study

19.5 Recording and Processing of Data

If using hard copies of CRF's, study center personnel will complete individual CRF's in black ink. All corrections to entered data will be made by drawing a single line through

the information to be corrected without obscuring it. All corrections will be initialed, dated and explained, if necessary. The use of "white-out" or obscuring correction tape will be prohibited. A CRF is required for every patient who received any amount of study treatment. The investigator will ensure that the CRF's are accurate, complete, legible and timely. Separate source records are required to support all CRF entries except those for which use of the CRF as source document is clearly allowed per note in the investigator study file.

Data must be submitted according to the protocol requirements for ALL patients registered. Patients for whom documentation is inadequate to determine eligibility will generally be deemed ineligible.

19.6 Non-Protocol Research

No investigative procedures other than those described in this protocol will be undertaken on the enrolled subjects without the agreement of the IRB.

19.7 Ethics

The investigator agrees to conduct the study in compliance with the protocol, current good clinical practices, and all applicable (local, FDA) regulatory guidelines and standard of ethics.

UM Ethics Programs' Research Ethics Consultation Service (RECS) is a free resource for UM Researchers. See the website for further information: http://www.miami.edu/index.php/ethics/projects/recs/

19.8 Essential documents for the conduct of a clinical trial

Essential documents are those documents with individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced. The following documents should be on file: 1) 1572 or investigator's agreement (for studies involving IND drugs or devices, respectively); 2) CV's and license of all Investigators; 3) IRB documentation/correspondance and 4) Documentation of IRB certification

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APPENDIX A: EXPEDITED ADVERSE EVENT (AE) REPORTING REQUIREMENTS

For all AEs that meet criteria for expedited reporting, the Principal Investigator (PI) is obligated to pursue and provide follow-up reporting information until the event has resolved or until an acceptable medical endpoint has been reached (i.e. for the duration specified in the protocol), or the patient is lost to follow-up.

The PI and all applicable research study team members should become familiar with the safety profile of the investigational agent(s) and/or intervention at the start of the study and for the duration of the research, e.g. by reviewing the Investigator's Brochure (IB) and any Safety Reports released, by the Sponsor as applicable.

A. FDA Expedited Reporting

   a. Sponsor-Investigators i.e. IND Holders, have additional reporting requirements to the FDA and other committees, and should consult the applicable regulations and agency guidelines for these requirements.

   b. Since this protocol involves the use of FDA IND agent(s), completion of the FDA MedWatch 3500A Reporting Form is required for Sponsor-Investigators. The Form can be obtained electronically at: http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM048334.pdf

      i. All serious, unexpected (unanticipated) and suspected adverse events must be directly reported to the FDA within 15 calendar days of being made known to the Principal Investigator (PI).

      ii. All fatal or life-threatening AEs must be directly reported to the FDA within 7 calendar days of being made known to the PI.

   c. For more information regarding reporting to the FDA, please refer to the FDA website for REPORTING GUIDELINES: http://www.fda.gov/Safety/MedWatch/HowToReport/default.htm

B. IRB Expedited Reporting

   a. All Investigators should also be aware of local Institutional requirements for AE reporting. For more information regarding the IRB policy, please refer to the UM HSRO's Investigator Manual: http://hsro.med.miami.edu/documents/HRP-103_-_INVESTIGATOR_MANUAL_4.11.2014.docx and the UM HSRO SOP on New Information (HRP-024) https://eprost.med.miami.edu/eProst/Doc/0/HLJ5OTJVQEH419E0I6QPT3B199/HRP-024%20-%20SOP%20-%20New%20Information.docx

   b. All AEs that are serious, unanticipated and possibly related will be reported to the IRB within ten (10) working days of being made known to the PI.

c. Events that are more frequent than anticipated or more severe than expected must be reported to the IRB within ten (10) working days of being made known to the PI.

d. All unanticipated deaths must be reported to the IRB within 24 hours of being made known to the PI.

C. Merck Expedited Reporting, (Events of Clinical Interest or ECIs)

a. In addition to the mandatory MedWatch 3500A Form, the PI is also required to comply with all reporting requirements as supplied by the Investigational Drug Sponsor: Merck.

b. 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.

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

d. 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.

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

f. 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.

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

APPENDIX B: DATA SUBMISSION SCHEDULE

CASE REPORT FORM(S)	TIMEPOINT TO BE COMPLETED
Pre-Treatment	
ICF, including HIPAA signed/dated	Prior to registration
Eligibility Checklist	
SCCC Protocol Enrollment Form	
On-study Form	Within 30 days of registration
On Treatment	
Treatment Form Cycle X, Day Y	Due every cycle for phase II-IV studies
End of Treatment	
Off Treatment Form	Within 14 days of discontinuation/completion of protocol therapy
Follow-Up (for studies with long term follow-up)	
Follow-up Form	Every 3 months until documented disease progression, death, withdrawal of consent, or EoS, whichever occurs first.
Progression/Relapse	Within 4 weeks of knowledge of progression/relapse
Notice of Death Form	Within 4 weeks of knowledge of death
Subsequent Malignancy	Within 4 weeks of knowledge of another malignancy

APPENDIX C: PERFORMANCE STATUS SCALES

PERFORMANCE STATUS CRITERIA					
ECOG (Zubrod)		**Karnofsky**		**Lansky**	
Score	Description	Score	Description	Score	Description
0	Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.	100	Fully active, normal.
		90	Able to carry on normal activity, minor signs or symptoms of disease.	90	Minor restrictions in physically strenuous activity.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.	80	Normal activity with effort, some signs or symptoms of disease.	80	Active, but tires more quickly.
		70	Cares for self, unable to carry on normal activity or do active work.	70	Both greater restriction of, and less time spent in, play activity.
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.	60	Up and around, but minimal active play; keeps busy with quieter activities.
		50	Requires considerable assistance and frequent medical care.	50	Gets dressed, but lies around much of the day; no active play; able to participate in all quiet play and activities.
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.	40	Mostly in bed, participates in quiet activities.
		30	Severely disabled, hospitalization indicated. Death not imminent.	30	In bed, needs assistance even for quiet play.
4	Completely disabled. Cannot carry on any selfcare. Totally confined to a bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.	20	Often sleeping, play entirely limited to very passive activities.
		10	Moribund, fatal processes progressing rapidly.	10	No play, does not get out of bed.
5	Dead	0	Dead	0	Dead

As published in Am J Clin Oncol: Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbone PP. Toxicity and Response Criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5:649-655. The Eastern Cooperative Oncology Group, Robert Comis, MD, Group Chair.

APPENDIX D: NYHA CLASSIFICATION OF HEART DISEASE

New York Heart Association (NYHA) classification of heart disease

NYHA Class	Symptoms
I	No symptoms and no limitation in ordinary physical activity, e.g. shortness of breath when walking, climbing stairs etc.
II	Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.
III	Marked limitation in activity due to symptoms, even during less-than-ordinary activity, e.g. walking short distances (20–100 m). Comfortable only at rest.
IV	Severe limitations. Experiences symptoms even while **at rest**. Mostly bedbound patients.

APPENDIX E: INFORMATION ON POSSIBLE DRUG INTERACTIONS

(NO formal pharmacokinetic drug interaction studies have been conducted with pembrolizumab.)

APPENDIX F: OPTIONAL BIOMARKER, CORRELATIVE AND SPECIAL STUDIES

Tumor tissue (obtain either from archival tissue or newly obtained at time of biopsy) may be stained for PD-L1 expression. Obtaining tumor tissue for correlative studies is optional and will only be performed at Screening for patients who consent. We will assess PD-L1 tumor expression with clinical outcome. This is exploratory and there is no formal statistical analysis planned. PD-L1 testing will be performed by Dr Monica Garcia-Buitrago at Jackson Memorial Hospital.

Peripheral blood will have serum obtained for biomarkers. Immunologic markers including ctDNA (approximately up to 30 mL using 2 green top tubes + 1 red top tube + 1 EDTA tube) will be performed. Hepatitis B and C viral titers (7 mL) will also be performed. Blood will be drawn at baseline, during treatment and/or at the time of documented disease progression and at treatment discontinuation, only on those patients who consent. Please refer to Section 13.0 for details.

The purpose is to determine if viral titers change with treatment. This is exploratory and no formal statistical analysis is planned. Biomarker testing will be performed by Dr. Niramol Savaraj at the following location:

University of Miami
1201 NW 16th St, Room D1010
Miami, FL 33125
Telephone: 305-575-3143
Email: nsavaraj@med.miami.edu

Several representative cytokines associated with T cell activation and suppression in serum, tumor biopsy and PBMCs from patients will also be analyzed pre-and post- anti-PD-1 treatment. T cell proliferation and activation in response to T cell receptor (TCR) and CD28 signals require IL-2, IL-12, IFN-r stimulation, but can be suppressed by immunosuppressive cytokines such as IL-10 and TGF-β.

1) Patient serum and peripheral blood myeloid cells (PBMCs) preparation:

We will collect the blood samples from patients including pre-treatment and post-treatment (30 cases). The whole blood samples will be centrifuged at 1, 200 rpm, and then supernatant (serum) will be collected and stored at -80 degree for biomarker screening. The rest of blood samples (pellets) will be mixed with phosphate-buffered saline (PBS, 1:1) and added on top of Ficoll-Paque (GE Healthcare Life Science); PBMC will be separated by centrifuging at 100 x g.

2) Detection of IL-12, IL-10, and TGF-β in patent serum:

As mentioned, patient serum (including pretreatment and post-treatment) will be stored at -80 degree and TGF-β, IL-12 and IL-10 levels in serum will be detected using ELISA. Thereafter, we will correlate the levels of these cytokines with tumor progression, T cell activity in PBMCs, and activation of tumor infiltrating lymphocytes (TILs, CD3+ cells), and PD-L1 expression. The

detection of T cell activation will be based on IFN-r, IL-2, and IL-12 expressions in PBMC (or CD3+ T cells).

3) Detection of IFN-r, IL-2, and IL-10 expressions in PBMCs using intracellular staining:

After we obtain PBMC, we will plate PBMC (1 x105) in 96-well plate and incubate them with brefeldinA overnight, and then fixed with 4% formalin and permeabilized by 0.5% saponin. Thereafter, cell will be incubated with anti-CD3, INF-r, IL-2, or IL-10 antibodies conjugated with fluorescence, and then analyzed by FACS. Positive control will be PBMCs treated with ionomycin and PMA to promote T cell activation, such IFN-r production.

4) Detection of IL-10, CD3, PD-L1, IFN-r, and IL-2 in tumor biopsy using IHC staining:

In this regard, we will obtain tumor biopsy from patients, either archived or fresh tumor if available (and patient is willing) and stain these markers to clarify that they express in TILs or cancer cells. Therefore, we will do single staining for each marker and double staining to co-localize CD3 and IL-2 /or IFN-r.

This testing will be performed by Dr. Niramol Savaraj at the following location:

University of Miami
1201 NW 16th St, Room D1010
Miami, FL 33125
Telephone: 305-575-3143
Email: nsavaraj@med.miami.edu

Approximately 10 ml blood in one EDTA tube will be collected along with the immunologic markers at the same time. The blood will be centrifuged, plasma and cells separated and sent for sent to Merck for tDNA testing.

APPENDIX G: CHILD-PUGH CLASSIFICATION

	Points*		
	1	2	3
Encephalopathy	None	Grade 1-2 (or precipitant-induced)	Grade 3-4 (or chronic)
Ascites	None	Mild/Moderate (diuretic-responsive)	Severe (diuretic-refractory)
Bilirubin (mg/dL)	<2	2-3	>3
Albumin (g/dL)	>3.5	2.8-3.5	<2.8
PT (sec prolonged) or INR	<4 <1.7	4-6 1.7-2.3	>6 >2.3

CTP score is obtained by adding the score for each parameter
CTP class: A = 5-6 points
B = 7-9 points
C = 10-15 points

Reference: The U.S. Department of Veterans Affairs
http://www.hepatitis.va.gov/provider/tools/child-pugh-calculator.asp

APPENDIX H: PROTOCOL APPROVED METHODS OF CONTRACEPTION

Pembrolizumab

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

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 the protocol. 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.

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

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

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

APPENDIX I: EVENTS OF CLINICAL INTEREST & SUPPORTIVE CARE GUIDELINES FOR PEMBROLIZUMAB

Suggested supportive care measures for the management of AEs with potential immunologic etiology. Where appropriate, these guidelines include the use of oral or intravenous treatment with corticosteroids as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. These guidelines are intended to be applied when the Investigator determines the events to be related to pembrolizumab.

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

- **Diarrhea/Colitis**:
  Subjects should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus).
    - All subjects who experience diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion. For Grade 2 or higher diarrhea, consider GI consultation and endoscopy to confirm or rule out colitis.
    - For **Grade 2 diarrhea/colitis** that persists greater than 3 days, administer oral corticosteroids.
    - For **Grade 3 or 4 diarrhea/colitis** that persists > 1 week, treat with intravenous steroids followed by high dose oral steroids.
    - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

- **Type 1 diabetes mellitus or T1DM (if new onset, including diabetic ketoacidosis [DKA]) or ≥ Grade 3 Hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis (DKA)**
    - For **T1DM** or **Grade 3-4** Hyperglycemia
        - Insulin replacement therapy is recommended for Type I diabetes mellitus and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria.
        - Evaluate patients with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.

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

Replacement of appropriate hormones may be required as the steroid dose is tapered.

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

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

- **Hepatic**:
  - For **Grade 3** events, monitor liver function tests more frequently until returned to baseline values (consider weekly).
    - Treat with IV or oral corticosteroids
  - For **Grade 4** events, treat with intravenous corticosteroids for 24 to 48 hours (or longer if clinically indicated). Monitor LFTs labs at least weekly until Grade 0-1 or baseline at Investigator discretion.
  - When symptoms improve to Grade 2 or less, a steroid taper should be started and continued over no less than 4 weeks.
  - Hold drug if an elevated AST or ALT lab value that is ≥ 5X the upper limit of normal (ULN) **and** an elevated total bilirubin lab value that is ≥ 2X the ULN **and**, at the same time, an alkaline phosphatase lab value that is < 2X the ULN, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.* Monitor labs tests more frequently until AST, ALT and total bilirubin values return to baseline or <grade 3.

    *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).

- **Renal Failure or Nephritis**:
  - For **Grade 2** events, treat with corticosteroids.

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

- **Overdose**: An overdose that is not associated with clinical symptoms or abnormal laboratory results.

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

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

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

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

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

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	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab (MK-3475) with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic).

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
	(e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. **Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.**	
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.		

REFERENCE: Merck. *Pembrolizumab Program (MK-3475) Event of Clinical Interest Guidance Document*. Version 5.0. 18-Dec-2014.

APPENDIX J: PREPARATION AND ADMINISTRATION/ RECONSTITUTION OF PEMBROLIZUMAB (KEYTRUDA®) FOR INJECTION (LYOPHILIZED POWDER)*

Reconstitution

- Add 2.3 mL of Sterile Water for Injection, USP by injecting the water along the walls of the vial and not directly on the lyophilized powder (resulting concentration 25 mg/mL).

- Slowly swirl the vial. Allow up to 5 minutes for the bubbles to clear. Do not shake the vial.

Preparation for Intravenous Infusion

- Visually inspect the solution for particulate matter and discoloration prior to administration. The solution is clear to slightly opalescent, colorless to slightly yellow. Discard the vial if visible particles are observed.

- Dilute KEYTRUDA injection (solution) or reconstituted lyophilized powder prior to intravenous administration.

- Withdraw the required volume from the vial(s) of KEYTRUDA and transfer into an intravenous (IV) bag containing 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP. Mix diluted solution by gentle inversion. The final concentration of the diluted solution should be between 1 mg/mL to 10 mg/mL.

- Discard any unused portion left in the vial.

Storage of Reconstituted and Diluted Solutions

The product does not contain a preservative. Store the reconstituted and diluted solution from the KEYTRUDA 50 mg vial either:

- At room temperature for no more than 6 hours from the time of reconstitution. This includes room temperature storage of reconstituted vials, storage of the infusion solution in the IV bag, and the duration of infusion.

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

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

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

- Under refrigeration at 2°C to 8°C (36°F to 46°F) for no more than 24 hours from the time of dilution. If refrigerated, allow the diluted solution to come to room temperature prior to administration. Do not freeze.

***Reference**: Prescribing Information for pembrolizumab injection (Keytruda®).