COLUMBIA UNIVERSITY MEDICAL CENTER

Herbert Irving Comprehensive Cancer Center Protocol

Phase II Open-Label, Single-Center Study Evaluating Safety and Efficacy of Pembrolizumab Following Induction with the Hypomethylating Agent Azacitidine in Patients with Advanced Pancreatic Cancer After Failure of First-Line Therapy

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TITLE: Phase II Open-Label, Single-Center Study Evaluating Safety and Efficacy of Pembrolizumab Following Induction with the Hypomethylating Agent Azacitidine in Patients with Advanced Pancreatic Cancer After Failure of First-Line Therapy.

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PROTOCOL SIGNATURE PAGE
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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 (or Manufacturer's Brochure) regarding the risks and potential benefits. I will promptly submit the protocol to the applicable IRB for review and approval. Once the protocol has been approved by the IRB, I understand that any modification made during the course of the study must first be approved by the IRB, prior to implementation except when such modification is made to remove an immediate hazard to the subject. I certify that I, and the study staff, have received the requisite training to conduct this research protocol. I agree to maintain adequate and accurate records in accordance with Columbia University and Herbert Irving Comprehensive Cancer Center policies, Federal, state and local laws and regulations. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

Instructions to Principal Investigator: Sign and Date this signature page and print your name.
Return the original, completed and signed to the Clinical Protocol & Data Management Office.
Retain a copy in the regulatory binder.

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Signature of Principal Investigator Date

_____

Principal Investigator Name (Print)

_____

Name of Institution

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1. PROTOCOL SYNOPSIS

This document is a protocol for a human research study. This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Columbia University Medical Center institutional research policies and procedures.

Title	Phase II open-label, single-center study evaluating safety and efficacy of pembrolizumab following induction with the hypomethylating agent azacitidine in patients with locally advanced or metastatic pancreatic cancer after failure of first-line therapy.
Protocol Number	AAAR3554
Trial Phase	2
Methodology	This is a single arm, open-label phase II trial of combination azacitidine and pembrolizumab in patients with locally advanced or metastatic pancreatic cancer in order to evaluate safety and efficacy. The primary endpoint is progression-free survival.
Study Duration	We estimate that the trial will require approximately 24 months to complete, with up to 18 months accrual and an additional 6 months follow-up to evaluate the primary efficacy outcomes for all subjects.
Study Center(s)	Columbia University Medical Center
Objectives	1. Primary objective: To evaluate the progression-free survival per RECIST 1.1. 2. Secondary Objectives: a. Safety Objective: To determine the safety and tolerability of induction therapy with azacitidine followed by pembrolizumab in advanced pancreatic cancer. b. To evaluate the overall response rate (ORR), duration of response (DOR), disease control rate (DCR), and time to progression (TTP) per RECIST 1.1, and OS.
Number of Subjects	31 evaluable subjects will be enrolled overall
Diagnosis and Main Inclusion Criteria	Locally advanced or metastatic pancreatic cancer who progressed on a single line of 5-FU- or gemcitabine-based chemotherapy.
Study Product, Dose, Route, Regimen	• Pembrolizumab 200 mg IV every 3 weeks until progression • Azacitidine 50 mg/m2 subcutaneous daily for 5 days every 28 days

Duration of administration	Treatment will continue until progressive disease, unacceptable adverse events, intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw the subject, subject withdrawal of consent, pregnancy of the subject, noncompliance with trial treatment or procedure requirements, subject receives 35 treatments (approx. 2 years) of pembrolizumab, or administrative reasons requiring cessation of treatment.
Reference therapy	Not applicable – Single arm study.
Statistical Methodology	This is a single arm, phase II study. To detect an improvement in progression free survival from a historical control of 2 months to 4 months, with a one-sided p-value of 0.05 and 80% power, 31 evaluable patients will be required. We anticipate accrual over 18 months with an additional 6 months required for follow-up.

1.1. Trial Design Overview

This is a single-arm, single-center, open-label trial of azacitidine combined with pembrolizumab in subjects with locally-advanced or metastatic pancreatic adenocarcinoma. Thirty-one evaluable subjects will be enrolled to assess the efficacy and safety of combination therapy in the second- line setting.

All subjects will have received systemic first-line chemotherapy, 5-FU or gemcitabine-based combination or monotherapy, prior to enrollment on the study. Azacitidine daily for 5 days will be given every 4 weeks (28 days). Fixed-dose pembrolizumab will be administered every 3 weeks for up to approximately 2 years beginning 2 weeks after initiation of azacitidine. The primary efficacy endpoint will be progression-free survival among all enrolled subjects. Disease progression will be determined based on RECIST 1.1 criteria; however, patients will be permitted to continue therapy following the development of progression of disease by RECIST 1.1 criteria if considered clinically appropriate by the study principal investigator.

As preliminary data suggests there is minimal toxicity overlap between pembrolizumab and a hypomethylating agent, there will be an accelerated Phase 1 dose determination component of the study. In the initial cohort, low-dose azacitidine will be administered, as studied in patients with advanced or metastatic solid tumors,[1] and pembrolizumab will be administered at fixed dose
as detailed in the protocol. An initial cohort of 6 subjects will be enrolled, treated with combination therapy, and assessed for safety. Following enrollment of the initial 6 evaluable subjects all toxicity data will be reviewed. If 2 or more patients experience a treatment related dose-limiting toxicity (DLT) within the first 6 weeks of treatment administration (Defined in Section 5.2), then accrual at that dose level will stop. We will allow for 1 dose reduction in azacitidine and if agreed by the PI, the study will resume at the lower dose (Dose -1) and will again accrue 6 subjects who will receive combination therapy. If 2 or more subjects experience treatment related DLTs at this level, we will discontinue the combination study.

If the combination dose is deemed safe (≤ 1 DLT), the study will complete accrual with treatment of an additional 25 subjects at the safe combination dose. Adverse events will be monitored throughout the trial and graded in severity according to the guidelines in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. DLT is defined as a grade 3 or above toxicity according to the CTCAE version 4.0.

After the end of treatment, each subject will be followed by 30 days for adverse event monitoring. Serious adverse events and Events of Clinical Interest (ECI) will be collected for 90 days after the end of treatment or 30 days after the end of treatment if the subject initiates new anticancer therapy, whichever is earlier. Subjects who discontinue treatment for reasons other than disease recurrence will have post-treatment follow-up for disease status until disease recurrence, withdrawing consent, or becoming lost to follow-up. All subjects will be contacted by telephone every 3 months for overall survival until death, withdrawal of consent or the end of the study, whichever comes first.

Every subject enrolled will be required to have pre-treatment, biopsy-confirmed disease. Development of a predictive diagnostic assay that enables prospective identification of patients who are likely to respond to azacitidine plus pembrolizumab may allow for preselection of patients likely to benefit from treatment with these regimens in future clinical studies. To facilitate additional PD analysis, on-treatment biopsies will be required for all subjects after 8 weeks of therapy if felt to be clinically feasible by the treating physician. Tumor samples will be collected and analyzed for molecular changes that occur during treatment with azacitidine and pembrolizumab. These analyses will help elucidate early mechanisms of action, predictors of treatment response, and predictors of survival in pancreatic cancer. Changes in tumor-infiltrating T-cell activity, measured by expression of granzyme B and other exploratory makers, will be explored in freshly obtained tumor tissue prior to and during induction and maintenance treatment.

Changes in blood biomarkers may provide evidence for biologic activity of combination azacitidine and pembrolizumab in humans and may allow for the development of a blood-based biomarker to help predict which patients may benefit from priming with hypomethylation followed by PD-1 inhibition. An exploratory objective is to evaluate changes in pharmacodynamics markers, including methylation status.

This study will be conducted in conformance with Good Clinical Practices.

Specific procedures to be performed during the trial, as well as their prescribed times and associated visit windows, are outlined in the Trial Flow Chart – Section 12.1.

1.2. Trial Schema

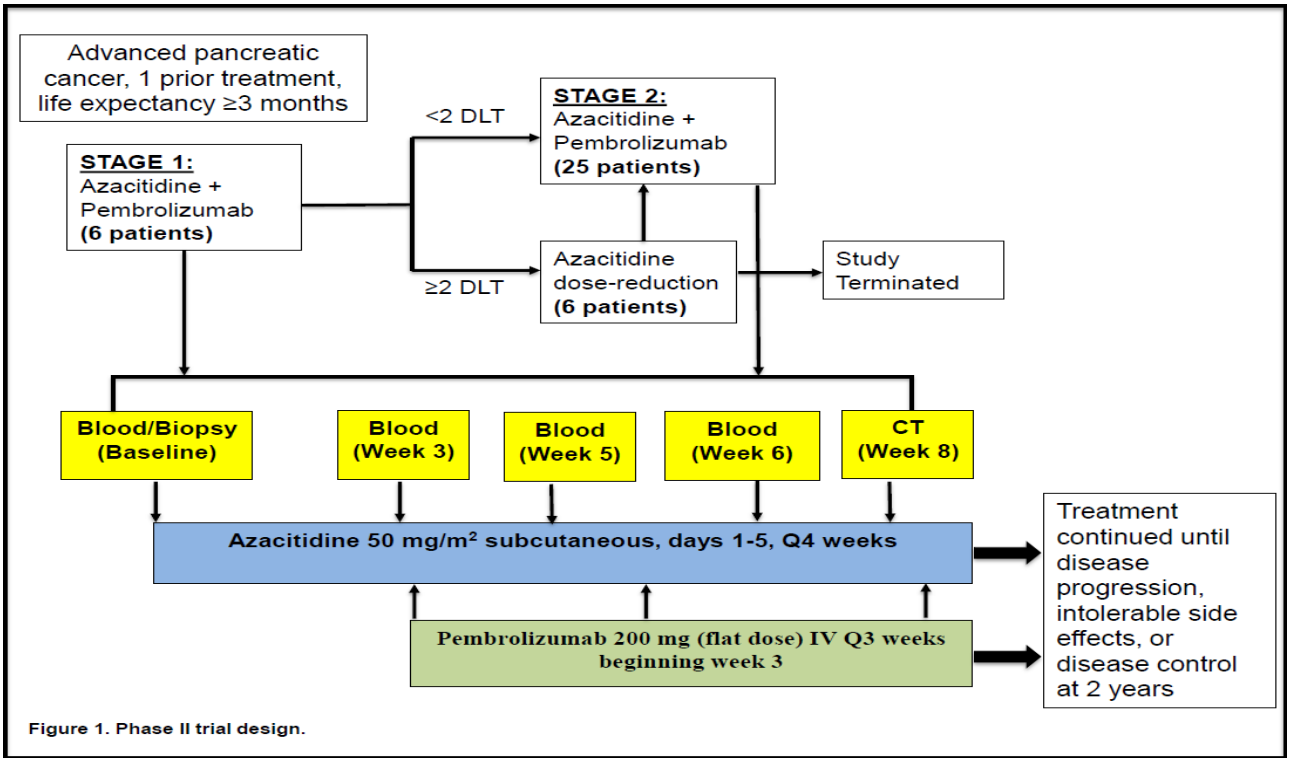

Figure 1. Phase II trial design.

2. STUDY OBJECTIVES

We will conduct a clinical trial of azacitidine combined with pembrolizumab in patients with advanced pancreatic cancer who progressed on first-line systemic therapy.

2.1. Primary Objective & Hypothesis

Objective: To evaluate the progression-free survival (PFS) per RECIST 1.1.
Hypothesis: We hypothesize that anti-tumor immunity can be achieved in pancreatic adenocarcinoma and that combining hypomethylation with PD-1 blockade will alter gene signature pathways and shift the immune milieu to enhance immune activation leading to delayed time to death or progression in subjects with pancreatic adenocarcinoma.

2.2. Secondary Objectives & Hypothesis

Safety and Tolerability Objective: To determine the safety and tolerability of azacitidine combined with pembrolizumab in advanced pancreatic cancer.
Hypothesis: We hypothesize that azacitidine priming in conjunction with pembrolizumab will

be safe and tolerable and will delay progression of pancreatic cancer.

Efficacy Objective: To evaluate the overall response rate (ORR), duration of response (DOR), disease control rate (DCR) per RECIST 1.1, and overall survival (OS).

Hypothesis: We hypothesize that combination hypomethylation with PD-1 blockade will enhance immune activation and lead to high response rates, longer periods of response, improve disease control, and prolonged survival compared to historical controls.

2.3. Exploratory Objectives & Hypothesis Objectives:

- To explore the relationship between response rate and tumor-infiltrating lymphocytes and macrophage tumor infiltration within the tumor and the tumor microenvironment from pre- versus on-treatment biopsies.
- To evaluate the methylation status within tumor and peripheral blood.
- To identify molecular (genomic, metabolic, and/or proteomic) determinants of response or resistance (e.g. PD-L1, gene expression profiling, or genomic variation), using blood and/or tumor tissue to define novel predictive and pharmacodynamics biomarkers and better understand the mechanism of action of pembrolizumab.

Hypothesis: We hypothesize that baseline markers of immune activation will correlate with response to pembrolizumab and that responders to pembrolizumab will have distinct tumor immune phenotype and gene expression profiling compared to non-responders.

3. BACKGROUND & RATIONALE

3.1. Pancreatic Cancer Background

Pancreatic ductal adenocarcinoma (PDA) has the worst prognosis of any major malignancy in the United States and, unlike other common cancers, annual deaths from PDA are rising. During the year 2014, it was estimated that 46,420 people would be diagnosed with PDA and approximately 39,590 people would die in the U.S.[2] Despite recent advances, cytotoxic chemotherapy for PDA has been disappointing with response rates of 20-30% for the most active regimens[3] and little activity for targeted therapies. Even among the small subset of patients who are suitable for surgical resection at the time of diagnosis, complete resection is followed by recurrence in >90% of patients without further systemic therapy, with a median time to recurrence of 6.9 months.[4] Thus all PDA patients require systemic chemotherapy and more effective regimens are urgently needed.[5]

Combination chemotherapy is effective in controlling disease and prolonging survival in patients with advanced pancreatic cancer. Despite recent successful phase 3 studies in the first-line setting, there is no defined second-line treatment for patients who experience disease progression following first-line therapy. Consensus guidelines (such as the NCCN guidelines) recommend clinical trial participation in this setting. The median progression-free and overall survival for second-line therapy has been disappointing with a recent randomized cooperative group study (SWOG S1115[6]) resulting in a median PFS of 2 months in the control group.

3.2. Immunotherapy Background

Immune checkpoint inhibitors have recently emerged as an important treatment modality for a variety of malignancies. Immune responses directed against tumors are one of the body's natural defense against the growth and proliferation of cancer cells. T cells play a critical role in antitumor immunity and their infiltration and activity have been linked to improved

prognosis
in a number of cancers.[7,8] T-cells are activated when the T-cell receptor (TCR) recognizes tumor antigens bound to major histocompatibility complex proteins on antigen-presenting cells (APCs). This interaction leads to differentiation of T-cells into antitumor effectors that are capable of destroying cancer cells expressing the cognate antigen. An additional costimulatory signal is also necessary for T-cell activation, which is provided by the interaction between CD28 (on the T- cell) and B7 proteins (CD80 or CD86 on APCs). Once activated, T-cells upregulate inhibitory (checkpoint) molecules, which attenuate and eventually terminate the T-cell response. Over time
and under pressure from immune attack, cancers develop strategies to evade immune-mediated killing allowing them to develop unchecked. Immune evasion can occur via a wide range of mechanisms and is now recognized as one of the hallmarks of cancer. One such mechanism involves exploitation of immune checkpoint molecules to suppress anti-tumor T-cell activity.

Programmed cell death ligand 1 (PD-L1) is another checkpoint protein and is upregulated in a broad range of cancers with a high frequency – up to 88% expression in some tumor types. In a number of these cancers, including lung,[9] renal,[10-12] pancreatic,[13,14] ovarian cancer[15], and hematologic malignancies,[16,17] tumor cell expression of PD-L1 is associated with reduced survival and an unfavorable prognosis.

PD-L1 is part of a complex system of receptors and ligands that are involved in controlling T- cell activation. PD-L1 acts at multiple sites in the body to help regulate normal immune responses and is utilized by tumors to help evade detection and elimination by the host immune system tumor response. In the lymph nodes, PD-L1 on antigen-presenting cells binds to PD-1 or CD80 on activated T cells and delivers an inhibitory signal to the T cell.[18,19] This results in reduced T-cell activation and fewer activated T cells in circulation. In the tumor microenvironment, PD-L1 expressed on tumor cells binds to PD-1 and CD80 on activated T cells reaching the tumor. This delivers an inhibitory signal to those T cells, preventing them from killing target cancer cells and protecting the tumor from immune elimination.[20]

Tumor types characterized as being responsive to immunotherapy-based approaches include melanoma,[21] renal cell carcinoma,[22] urothelial carcinoma,[23] malignant mesothelioma,[24] classical Hodgkin lymphoma, and non-small cell lung cancer.[25] Both nivolumab and pembrolizumab are approved for advanced melanoma and advanced NSCLC refractory to first-line chemotherapy.[26- 30] Pembrolizumab is also approved in NSCLC for two other indications: as first-line treatment for metastatic NSCLC with expression of PD-L1 on at least 50% of tumor cells, and to be used with pemetrexed and carboplatin for patients with previously untreated advanced nonsquamous NSCLC regardless of whether their tumors express PD-L1[1] (Langer CJ et al. Lancet Oncol.
2016; 17(11):1497-1508). Additionally, pembrolizumab is approved for recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) after platinum-based chemotherapy regardless of PD-L1 staining. Recently, pembrolizumab was FDA-approved for patients with solid tumors that were mismatch repair deficient and microsatellite unstable

Despite the success of checkpoint inhibitors as single therapy in several cancers, treatment of patients with pancreatic cancer with these single agents has been ineffective. One difference

between tumors that have responded to checkpoint inhibitors and pancreatic cancer is the immune status of the tumor microenvironment.32 Cancers that respond to checkpoint inhibitors tend to be naturally infiltrated with effector lymphocytes while pancreatic cancer is characterized by a highly
immunosuppressive tumor microenvironment composed of multiple immunosuppressive regulatory cells.

3.3. Epigenetic Background

Gastrointestinal (GI) cancers possess high degrees of epigenetic dysregulation. Epigenetic changes, such as DNA methylation, in tumor cells control gene expression and are known to alter immune cell phenotype and function. Methylation of cytosine residues, at CpG sites that are unmethylated in normal tissue, is catalyzed by the DNA methyltransferases (DNMTs).[33,34] In many malignancies, CpG islands within promoters of tumor suppressor genes become abnormally hypermethylated and thereby silenced.[35,36] The global methylation pattern of the cancer genome is observed across many different cancer phenotypes and has a profound impact on genome-wide transcriptional regulation, ultimately creating an immunosuppressive environment that impairs endogenous tumor clearance and promotes evasion.

In pancreatic cancer, DNA methylation is a mechanism through which tumor suppressor genes such as *p16* are inactived.[37] In fact, evidence supports the notion that aberrant methylation takes place very early during the histopathological development of this neoplasia. The loss of *p16* expression in pancreatic intraepithelial neoplasia (PanIN) lesions has been reported in patients with chronic pancreatitis[38], suggesting that this modification may contribute to the predisposition of patients affected by this disease who transition to develop pancreatic cancer. DNA from 65 PanIN lesions was assessed for methylation status of 8 genes previously recognized to be abnormally hypermethylated in invasive pancreatic adenocarcinoma.[39] Methylation at any one of these genes was identified in 68%. Additionally, aberrant CpG island hypermethylation was observed at early stages of PanINs and the incidence progressively increased during neoplastic development.

Epigenetically modulated re-expression of silenced genes induces chemosensitization, and the use of epigenetic therapy to sensitize for immune therapy is also now emerging. A recent study showed that after treatment with low-dose 5-azacitidine in breast, ovarian, and colorectal cell line lines as well as primary tumors, 20% of all upregulated gene sets belonged to immunomodulatory pathways (e.g. interferon signaling, cytokines, antigen presentation, inflammation, and cancer testes antigens, and the commonly upregulated gene sets between the 3 cancer types.[40] In murine mouse model, checkpoint inhibition combined with 5-azacitidine and entinostat resulted in a striking improvement in mouse survival and tumor growth inhibition with complete eradication of large colon cancers.[41]

An important feature of pancreatic cancer is its low cellularity and surrounding desmoplastic reaction, highlighting the importance of the tumor microenvironment in the initiation and progression of pancreatic cancer. In one study, the use of hypomethylating agents successfully inhibited tumor progression in a stroma-rich mouse model of pancreatic cancer.

In summary, a novel approach to improve response rates with immune checkpoint blockade is the use of epigenetic therapy to "prime" the tumor and its microenvironment. Expression of critical immune-related genes can be restored with hypomethylating agents (HMAs), impairing tumor growth through a variety of mechanisms.

3.4. Rationale

3.5. Rationale for Combining Hypomethylating Agents with Immunotherapy

Cancer testis antigens (CTAs) are protein fragments that are derived from proteins normally only expressed during embryonic development or in immune privileged organs such as the testes and brain. Because they are not typically expressed in the thymus nor exposed to antigen presenting cells, they are recognized as foreign the human immune system and are able to stimulate an immune response.[42] For poorly understood reasons, these proteins and the fragment CTAs are commonly expressed by tumor cells and are thus a potential target for a tumor-specific immune response.

In some cancers, it has been shown that expression of CTAs can be epigenetically silenced via hypermethylation of gene promoters.[43] This phenomenon appears to be reversible, as increased CTA expression and enhanced immunogenicity in cancerous but not normal cells following HMA therapy has been demonstrated in several pre-clinical models and clinical trials.[40,44-49] Epigenetic alterations have also been found to silence antigen-presenting machinery genes and downregulate MHC class I expression on tumor cells.[44] Treatment with agents such as azacitidine (a DNMT inhibitor) has reversed this phenotype in various *in vitro* and *in vivo* models.[50] Most importantly, HMA therapy has the potential to enhance antitumor immune responses by upregulating checkpoint elements such as PD-L1 and PD-1. Recent work has demonstrated that hypermethylation of the PD-L1 gene promoter is associated with decreased PD-L1 expression on tumor cells,[51] and azacitidine has been shown to increase PD-L1 expression in NSCLC cell lines at both the transcript and protein level.[50] Bone marrow samples from patients with a variety of hematologic malignancies have confirmed that treatment with HMAs is followed by evidence of increased PD-1/PD-L1 signaling.[52] A recent study used an animal metastatic cancer model that is known to be resistant to treatment with immune checkpoint blockade. HMAs and histone deacetylating agents were successfully used to reverse this resistance, presumably by depleting myeloid derived suppressor cells (MDSCs) within the tumor microenvironment.[41]

In summary, given that epigenetic dysregulation is present in pancreatic cancer and that epigenetic modifiers induce sensitization to immune therapy, there is strong pre-clinical and clinical rationale to investigate the combination of induction with a hypomethylating agent followed by checkpoint inhibition. In this trial, subjects will be treated with azacitidine, a DNMT inhibitor, and pembrolizumab in a sequential fashion.

3.6. Rationale for the Combination in Pancreatic Cancer

Our pre-clinical data suggests that decitabine treatment in the KPC model of pancreatic cancer leads to a significant upregulation of interferon-related genes and a polarization of the infiltrating immune cells.[53] We identified a shift towards a favorable macrophage phenotype

(M1 vs M2) and an increase in tumor infiltrating CD8 T cells. Based on these results we have evaluated the effect of single agent decitabine or anti-PD1H (a homologue of PD1 with very similar function and expression pattern) compared to combination therapy (treatment with decitabine followed by PD1 blockade). Our preliminary results showed minimal effect of either agent alone on tumor growth but marked decrease in tumor progression in the combination arm. These results form the foundation of this phase II study.

This study will treat patients with a combination of azacitidine and pembrolizumab. A direct comparison of azacitidine and decitabine, in terms of efficacy within a controlled clinical trial, has not been performed thus far. In randomized MDS trials, the remission rates were similar for azacitidine and decitabine but the overall survival in the experimental arm was significantly shorter in the decitabine trial compared to the azacitidine trial.[54,55] A primary reason to utilize azacitidine in this setting is our desire to utilize reduced dose therapy with the goal of maintaining subjects on therapy for as long as tolerated. Low-dose azacitidine is being tested in phase I/II clinical trials for advanced solid tumors—mainly colorectal cancer, small-cell lung carcinomas, ovarian cancer, and breast cancer. Furthermore, low-dose azacitidine with the HDAC inhibitor etinostat in refractory advanced non-small cell lung cancer was well-tolerated and led to impressive results in a subset of patients.[56]

3.7. Selected Subject Population

This study will enroll subjects with advanced pancreatic cancer who have progressed on first line chemotherapy. This is a population with few good therapeutic options beyond first line chemotherapy. Current guidelines and clinical practice recommend clinical trial as a preferred option for this patient population. This study will enroll eligible patients in the second-line setting irrespective of PD-L1 status, however, this will be checked in the baseline tumor specimens.

3.8. Rationale for Dose Selection/Regimen/Modification

Low-dose azactidine, as used in conjunction with cytotoxic chemotherapy for solid tumors, will be given in combination with fixed dose pembrolizumab as detailed in Section 4.1.3.

3.9. Rationale for Endpoints

3.10. Efficacy Endpoints

The primary efficacy objective of this study is to evaluate anti-tumor activity of pembrolizumab in combination with azacitidine as measured by progression-free survival. Additional efficacy endpoints will be assessed, most notably overall response rate and overall survival.

3.11. Safety Endpoints

The primary safety objective of this trial is to characterize the safety and tolerability of pembrolizumab in combination with azacitidine in subjects with locally-advanced or metastatic pancreatic cancer. The primary safety analysis will be based on subjects who experienced toxicities as defined by CTCAE (Appendix 2). Safety will be assessed by quantifying the toxicities and grades experienced by subjects who have received any study

drug, including serious adverse events (SAEs) and events of clinical interest (ECIs).

Safety will be assessed by adverse experiences using CTCAE, Version 4.0. The attribution to drug, time-of-onset, duration of the event, its resolution, and any concomitant medications administered will be recorded. Adverse events will be analyzed including but not limited to all adverse events (AE), SAEs, fatal AEs, and laboratory changes. Furthermore, specific events of clinical interest will be collected as described in Section 10.4.

3.12. Biomarker Research and Exploratory Endpoints

Additional biomarker research to identify factors important for azacitidine and pembrolizumab therapy may also be pursued. For example, tumor and blood samples (including serum and plasma) from this study may undergo proteomic, genomic, metabolomics, and transcriptional analyses. This research may evaluate factors important for predicting responsiveness or resistance to azacitidine and pembrolizumab therapy and other immunologic targets.

Both blood and tissue samples will be collected as available for these assays and patients will be asked to consent to use of any medically extra samples. Assays may include but are not be limited to the following:

3.13. Immunohistochemistry

PD-L1 expression in tumor tissue will be characterized by immunohistochemistry to explore the relationship between PD-L1 expression and response to treatment with pembrolizumab (this is a secondary objective of the trial). Other exploratory biomarkers (e.g. PD-1 expression, markers of T-cell phenotype) may also be evaluated.

3.14. Transcriptional Analyses

As an exploratory analysis, messenger RNA (mRNA) expression profiling in archival material (biopsy specimens, peripheral blood) will be completed to assess expression of approximately 500 genes and attempt to define a gene set critical for clinical response to pembrolizumab. The hypothesis to be tested is that pembrolizumab induces responses in tumors that reflect an inflamed/ immune phenotype based on gene expression signatures capturing PD -L1 & interferon gamma transcriptional programs. Global profiling will also be pursued. Expression of individual genes related to the immune system may also be evaluated such as immune signatures and critical cytokines (e.g., IL-10). MicroRNA profiling may also be pursued in serum samples.

3.15. Proteomic analysis

In addition to expression on the tumor tissue, PD-L1 can be shed from tumor and released into the blood. Enzyme-linked immunoassay can measure PD-L1 in serum and correlate this expression with response to pembrolizumab therapy, as well as levels of PD-L1 IHC or protein in the tumor. Blood would be a less invasive component from which to measure PDL1 protein biomarker. In addition to this specific protein biomarker, both tissue and blood derivatives can be subjected to proteomic profiling studies using a variety of platforms that could include but are not limited to immunoassay, Liquid Chromatography/Mass Spectrometry. This approach could identify novel protein biomarker that could aid in subject selection for pembrolizumab

therapy.

3.16. Gene Analyses

The application of new technologies, such as next generation sequencing, has provided scientists the opportunity to define certain tumor types at the genetic level as being 'hypermutated' or can detect the presence of specific T-cell clones within the tumor microenvironment or in the peripheral blood. There is a potential that the hypermutated state and/or increased T-cell clonality may correlate with response to pembrolizumab therapy, and/or that the converse, 'hypomutated' state or lack of dominant T-cell clones may correlate with non-response.

In addition, understanding genetic determinants of drug response is an important endeavor during medical research. This research will evaluate whether genetic variation within a clinical trial population correlates with response to the treatment(s) under evaluation. If genetic variations found to predict efficacy or adverse events, the data might inform optimal use of therapies in the subject population.

4. INVESTIGATIONAL AGENTS

4.1. Pembrolizumab

Pembrolizumab (MK-3475) 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, programmed death ligand 1 (PD-L1) and programmed death ligand 2 (PD-L2). KEYTRUDA® (pembrolizumab) has recently been approved in the United States for the treatment of patients with unresectable or metastatic melanoma and disease progression following treatment with ipilimumab or a BRAF inhibitor, if BRAF V600 mutation-positive. Pembrolizumab was also recently approved for the treatment of patients with metastatic non- small cell lung cancer (NSCLC) whose tumors express PD-L1 as determined by a Food and Drug Administration (FDA)-approved test, with disease progression on or after platinum- containing chemotherapy.

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades[57]. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies[58-61]. 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)[62].

The structure of murine PD-1 has been identified. 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-regulatory cells and natural killer cells[63]. 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[64-66]. 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 (PD-L1 or PD-L2) 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. 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.

4.1.1 Preclinical Data

Therapeutic studies in mouse models have shown that the administration of antibodies blocking the PD-1/PD-L1 interaction enhances infiltration of tumor-specific CD8+ T-cells and leads ultimately to tumor rejection, either as a monotherapy or in combination with other treatment modalities. Anti-mouse PD-1 and anti-mouse PD-L1 antibodies have demonstrated anti-tumor responses as monotherapy in models of squamous cell carcinoma, pancreatic carcinoma, melanoma, and colorectal carcinoma. Blockade of the PD-1 pathway effectively promotes CD8+ T-cell infiltration into the tumor and the presence of IFN-ɣ, granzyme B and perforin, indicating that the mechanism of action involved local infiltration and activation of

effector T-cell function in vivo[67,68]. Experiments have confirmed the in vivo efficacy of PD-1 blockade as a monotherapy as well as in combination with chemotherapy in syngeneic mouse tumor models (see the Investigator Brochure for additional details).

4.1.2 Clinical Data to Date

Clinical trials have demonstrated efficacy using pembrolizumab in subjects with advanced melanoma, non-small cell lung cancer (NSCLC), head and neck cancer, bladder cancer, Hodgkin's lymphoma, triple-negative breast cancer, and gastric adenocarcinoma. In addition, recent data demonstrate emerging evidence of single-agent activity in additional tumor types such as mesothelioma, urothelial cancer, ovarian cancer, neuroendocrine carcinoma, and small cell lung cancer.

4.1.3 Rationale for Dose Selection

The dose of pembrolizumab planned to be studied in this trial is 200 mg Q3W. Information on the rationale for selecting the 200 mg Q3W dose is summarized below.

Keynote-001, an open-label Phase I study, was conducted to evaluate the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics, and anti-tumor activity of single agent pembrolizumab. The dose escalation portion of this trial evaluated three dose levels, 1 mg/kg, 3 mg/kg and 10 mg/kg, administered every 2 weeks (Q2W) and dose expansion cohorts evaluated 2 mg/kg Q3W and 10 mg/kg Q3W in subjects with advanced solid tumors. All dose levels were well tolerated and no dose-limiting toxicities were observed. This first-in- human study of pembrolizumab showed evidence of target engagement and objective evidence of tumor size reduction at all dose levels. No maximum tolerated dose (MTD) has been identified. In addition, two randomized cohort evaluations of melanoma subjects receiving pembrolizumab at a dose of 2 mg/kg versus 10 mg/kg Q3W have been completed, and one randomized cohort evaluating 10 mg/kg Q3W versus 10 mg/kg Q2W has also been completed. The clinical efficacy and safety data demonstrate a lack of important differences in the efficacy and safety profiles across doses.

An integrated body of evidence, based on dose/exposure efficacy and safety relationships, demonstrated no clinically significant differences in efficacy and safety between doses of 200 mg or 2 mg/kg Q3W in patients with melanoma and NSCLC. As such, the recommended fixed dose is 200 mg Q3W.

The pharmacokinetics (PK) of pembrolizumab was characterized using a population PK analysis with concentration data collected from 2841 patients with various cancers who received pembrolizumab doses of 1 to 10 mg/kg Q2W or 2 to 10 mg/kg Q3W. The PK profile of pembrolizumab was consistent with that of other humanized monoclonal antibodies, which typically have a low clearance and a limited volume of distribution. The distribution of exposures from the 200 mg fixed dose overlapped with the 2 mg/kg dose and, importantly, maintained individual patient exposures within the exposure range established in melanoma and NSCLC associated with maximal clinical response. Pharmacokinetic properties of pembrolizumab, and specifically the weight-dependency in clearance and volume of distribution, were consistent with no meaningful advantage to weight -based dosing relative to fixed dosing.

In translating to other tumor indications, flat exposure-response relationships for efficacy and safety are observed, as the anti-tumor effect of pembrolizumab is driven through immune system activation rather than through a direct interaction with tumor cells, rendering it independent of the specific tumor type. In addition, available PK results in subjects with melanoma, NSCLC, and other tumor types support a lack of meaningful difference in pharmacokinetic exposures obtained at tested doses among tumor types. Thus, the 200 mg Q3W fixed-dose regimen is now considered an appropriate fixed dose for other tumor indications as well.

4.2. Azacitidine (Vidaza)

Azacitidine is a pyrimidine nucleoside analog of cytdidine. It is a metabolic inhibitor that promotes hypomethylation of DNA and restores normal gene differentiation and proliferation. Azacitidine is also directly cytotoxic to rapidly dividing cells and hematopoeietic cells in the bone marrow. Hypomethylation may promote episensitization to immunotherapy by immunogenicity priming, improving the tumor microenvironment, and enhancing gamma interferon sensitivity[40,50,69,70].

Despite encouraging results with demethylating agents in hematologic malignancy, single agent results in solid tumors have been disappointing. One of the historical reasons for this has been the use of cytotoxic doses which led to significant toxicity.[71] Since these initial studies, several recent pre-clinical and human studies have shown that much lower doses are sufficient to achieve a similar effect on methylation status without reaching doses that are associated with significant side effects. In solid tumors, treatment with demethylating agents such as decitabine or azacitidine has encouraging results when administered prior to cytotoxic chemotherapy.

In recent clinical trials for non-small cell lung cancer, a small number of patients had remarkably robust and durable responses to immune checkpoint blockade after first receiving azacitidine[50,56]. Azacitidine induces interferon signaling and concordant upregulation of surface antigens and their assembly proteins, viral defense pathways, and transcript and surface protein levels of PD- L1, the key checkpoint ligand targeted by pembrolizumab[40,50]. A recent study has demonstrated the effect of the demethylating agent, azacitidine, via upregulation of endogenous retroviruses which led to a growth-inhibiting tumor response[72]. These authors have shown a significantly increased efficacy of azacitidine plus anti-CTLA-4 therapy compared to anti-CTLA-4 therapy alone in a murine melanoma model.

The pharmacokinetics of azacitidine were studied in 6 myelodysplastic (MDS) patients following a single 75 mg/m^2 SubQ dose and a single 75 mg/m^2 IV dose. Azacitidine is rapidly absorbed after SubQ administration, and the bioavailability of SubQ azacitidine relative to IV azacitidine was approximately 89% based on area under the curve. It is FDA-approved for IV or SubQ administration in MDS.

Azacitidine for subcutaneous injection is supplied as a lyophilized powder in 100 mg single-dose vials. Each vial also contains 100 mg mannitol. For subcutaneous injection, reconstitute

azacitidine aseptically with 4 mL sterile water. Inject the diluent slowly into the vial. Vigorously shake or roll the vial until a uniform suspension is achieved. The suspension will be cloudy and should not be filtered after reconstituting since doing so could remove the active substance. The resulting suspension will contain azacitidine 25 mg/mL.

For immediate SubQ administration, doses greater than 4 mL should be divided equally into 2 syringes. The product may be held at room temperature for up to 1 hour, but must be administered within 1 hour after reconstitution. For delayed SubQ administration, the reconstituted product may be kept in the vial or drawn into a syringe. Doses greater than 4 mL should be divided equally into 2 syringes. The product must be refrigerated immediately. When azacitidine is reconstituted using water for injection that has not been refrigerated, the reconstituted product may be held under refrigerated conditions (2□C - 8□C , 36□F - 46□F) for up to 8 hours. When azacitidine is reconstituted using refrigerated (2□C - 8□C , 36□F - 46□F) water for injection, the reconstituted product may be stored under refrigerated conditions (2□C - 8□C ,

36□F - 46□F) for up to 22 hours. After removal from refrigerated conditions, the suspension may be allowed to equilibrate to room temperature for up to 30 minutes prior to administration. To provide a homogeneous suspension, the contents of the dosing syringe must be re-suspended immediately prior to administration.

Doses greater than 4 mL should be divided equally into 2 syringes and injected into 2 separate sites. Rotate sites for each injection (thigh, abdomen, or upper arm). New injections should be given at least one inch from an old site and never into areas where the site is tender, bruised, red, or hard. The recommended starting dose in MDS is 75 mg/m^2 SubQ, however, lower doses have been shown to be effective in solid tumor patients in conjunction with other chemotherapeutic agents. In this protocol, we will utilize lower starting dose of azacitidine (50 mg/m^2) in conjunction with pembrolizumab.

5. STUDY DESIGN

5.1. General Design

This is a single-arm, open-label, single site Phase II trial of azacitidine combined with pembrolizumab in previously systemically treated subjects with a histologically or cytologically confirmed diagnosis of pancreatic ductal adenocarcinoma. Pre-treatment biopsies will be required for those subjects without an archival sample. All subjects will be required to provide a tumor tissue sample, either from the primary or a metastatic site, for biomarker analysis after 8 weeks on treatment. Thirty-one evaluable subjects will be allocated to receive azacitidine 50 mg/m2 SubQ for 5 days every 28 days (Q4W) with single-agent pembrolizumab 200 mg IV every 3 weeks (Q3W) beginning on week 3.

The primary objective of this trial is to determine the PFS of pembrolizumab given in combination with a hypomethylating agent. Beginning with screening, all imaging assessments will be evaluated using RECIST 1.1. On-study imaging assessments will be performed every 8

weeks (Q8W) calculated from the date of allocation and independent of treatment delays. RECIST 1.1 will be used by the site for treatment decisions until the first radiologic evidence of progressive disease (PD).

Following the first radiologic evidence of PD by RECIST 1.1, treatment decisions may be made by the adaptation of RECIST 1.1 as described in Section 13.5 termed immune-related RECIST (irRECIST) to accommodate the tumor response patterns seen with pembrolizumab treatment (e.g., tumor flare). This was first described by Nishino, et al. 2013[73] and is further modified for the pembrolizumab program as described in Section 13.5. For a clinically stable subject with first radiologic evidence of PD, it is at the discretion of the principal investigator to continue treating the subject with pembrolizumab until PD is confirmed at least 4 weeks after the date of the first tumor imaging confirming PD per the principal investigator. If radiologic PD is confirmed by the subsequent tumor imaging, the subject should be discontinued from treatment unless, in the opinion of the investigator, the subject is achieving a clinically meaningful benefit; an exception for continued treatment may be considered following consultation with the PI.

Subjects may continue to be treated with pembrolizumab until PD is confirmed by RECIST 1.1, unacceptable adverse events (AEs), intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw the subject, subject withdrawal of consent, pregnancy of the subject, noncompliance with trial treatment or procedure requirements, administrative reasons, or the subject has received 35 trial treatments (approximately 2 years) with pembrolizumab. Subjects who discontinue trial treatment for a reason other than disease progression will move into the Follow-Up Phase and should be assessed every 8 weeks (±7 days) by radiologic imaging to monitor disease status.

Disease status will continue to be monitored until whichever of the following occurs first: the start of new anti-cancer treatment, disease progression, death, or the end of the study. All subjects will be followed by phone contact every 12 weeks (+/- 2 weeks) for overall survival (OS) until death, withdrawal of consent from participation in the study, or the end of the study, whichever comes first.

Subjects who attain a CR by 2 tumor imaging assessments at least 4 weeks apart and who have received at least 8 treatments (approximately 6 months of therapy) with pembrolizumab may discontinue treatment at the discretion of the investigator after receiving at least 2 treatments beyond the initial determination of a CR. Subjects who stop pembrolizumab after receiving 35 trial treatments (approx. 2 years) for reasons other than PD or intolerability or who stop after attaining a CR may be eligible for retreatment with up to an additional 17 treatments (second course of treatment, approximately 1 year) after they have experienced radiographic PD after consultation with the principal investigator. The decision to retreat will be at the discretion of the investigator only if no other cancer treatment was administered since the last dose of pembrolizumab, the subject still meets the parameters listed in the inclusion and exclusion criteria, and the trial remains open.

Adverse events will be monitored throughout the trial and graded in severity according to

the guidelines outlined in the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 (Appendix 2). After the end of treatment, each subject will be followed for 30 days for AE monitoring. Serious adverse events (SAEs) will be collected for 90 days after the end of treatment or 30 days after the end of treatment if the subject initiates new anticancer therapy, whichever is earlier.

This study will be conducted in conformance with Good Clinical Practices (GCP).

Specific procedures to be performed during the trial, as well as their prescribed times and associated visit windows, are outlined in the Trial Flow Chart - Section 12.1. Details of each procedure are provided in Section 12.2 – Trial Procedures.

5.2. Dose Limiting Toxicities

All toxicities will be graded according to the NCI CTCAE version 4.0 and assessed for relationship to study medications.

The incidence of DLT(s) assessed in the first 6 evaluable subjects during the first 6 weeks will be to initially determine whether the dose level of combination therapy is tolerable. A subject will be considered evaluable for DLT if they have received at least 1 dose of pembrolizumab after receiving the initial week of azacitidine. DLT should not be an AE considered by the investigator to be disease related. The following drug-related AE (whether related to one or both agents) will be considered a DLT:

- Any Grade ≥ 3 drug-related non-hematological AE, including the following laboratory abnormalities
  - If a subject has baseline Grade ≤ 1 AST, ALT, or total bilirubin, a drug-related Grade ≥ 3 toxicity will be considered a DLT
  - If a subject has baseline asymptomatic Grade 2 AST or ALT due to tumor infiltration in the liver, drug-related elevations in AST and/or ALT > 2x baseline or a maximum of > 8x ULN that does not resolve to Grade 2 or less within 48 hours (if symptomatic) or that does not resolve to Grade 1 or less within 3 weeks of onset (if asymptomatic) will be considered a DLT.

- Any Grade ≥ 3 drug-related non-hematological laboratory abnormality with the following exceptions:
  - Grade 3 abnormal laboratory result that is asymptomatic and lasts no longer than 72 hours.
  - Grade 4 lymphocytopenia not associated with symptoms or clinical manifestations

- Any toxicity managed by discontinuation of pembrolizumab (see section 9.1).
- Any toxicity managed by discontinuation of azacitidine (see section 9.2).
- Grade ≥ 3 thrombocytopenia with bleeding, and febrile neutropenia of any Grade.

5.3. Number of Patients

Thirty-one subjects who are evaluable for progression-free survival will be enrolled. Unevaluable patients (as defined in Section 13.1.1) will be replaced.

6. SUBJECT SELECTION AND WITHDRAWAL

Male and female subjects with advanced pancreatic ductal adenocarcinoma after progression on first-line systemic therapy who are considered incurable will be enrolled in this trial.

6.1. Inclusion Criteria

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

1. Be willing and able to provide written informed consent for the trial. In cases of partial impairment, impairment that fluctuates over time, or complete impairment due to dementia, stroke, traumatic brain injury, developmental disorders (including mentally disabled persons), serious mental illness, and delirium, a subject may be enrolled if the subject's legally authorized representative consents on the subject's behalf.

- Age ≥18 years of age on day of signing informed consent.
- Have histologically or cytologically confirmed diagnosis of pancreatic ductal adenocarcinoma
- Have a predicted life expectancy of greater than 3 months.
- Have measurable disease based on RECIST 1.1.
- Have a performance status of 0 or 1 using the ECOG Performance Scale within 3 days of first dose of study drug.
- Have documented radiographic progression to or documented intolerance of first line systemic chemotherapy which included at least gemcitabine or 5-FU based regimen (including capecitabine).
- Subjects who have documented disease recurrence within 6 months of completing neoadjuvant or adjuvant chemotherapy for limited disease will be eligible for study provided they have not received an additional line of systemic therapy. Subjects who recur greater than 6 months after completing adjuvant or neoadjuvant chemotherapy will not be eligible unless they receive additional chemotherapy for advanced disease.

- Have a negative urine or serum pregnancy test within 72 hours prior to receiving the first dose of study medication (Cycle 1, Day 1) (female subjects of childbearing potential). If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
- Be willing to use an adequate method of contraception for the course of the study through 120 days after the last dose of study medication (male and female subjects of childbearing potential [see Section 8.5.2]).

- Demonstrate adequate organ function as defined in Table 1.

Table 1. Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Leukocytes	≥2,000/mcL
Absolute neutrophil count (ANC)	≥1,500 /mcL
Platelets	≥100,000 / mcL
Hemoglobin	≥9 g/dL without transfusion or EPO dependency within 7 days
Renal	
Creatinine **OR** Measured or calculated[a] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 X upper limit of normal (ULN) **OR** ≥60 mL/min for subject with creatinine levels > 1.5 X institutional ULN
Hepatic	
Total bilirubin	≤ 2 mg/dL or direct bilirubin ≤ ULN for those with total bilirubin >2xULN Subjects with Gilbert Syndrome will be eligible if total bilirubin is < 3.0 mg/dL.
AST (SGOT) and ALT (SGPT)	≤ 2.5 X ULN **OR** ≤ 5 X ULN for subjects with liver metastases
Albumin	>3.0 mg/dL
Amylase and Lipase	≤1.5 ULN. Subjects with Amylase or Lipase > 1.5 ULN may enroll if there are neither clinical nor radiographic signs of pancreatitis
Coagulation	
INR or PT aPTT	≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or aPTT is within therapeutic range of intended use of anticoagulants

6.2. Exclusion Criteria

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

- Is currently participating and receiving study therapy or has participated in a study ofan investigational agent and received study therapy, or herbal/complementary oral or IV medicine within 2 weeks of the first dose of treatment.
- All toxicities attributed to prior anti-cancer therapy other than alopecia and fatigue must have resolved to Grade 1 (NCI-CTCAE Version 4.0) or baseline prior to administration of first dose of study drug. Subjects with toxicities attributed to prior anti-cancer therapy that are not expected to resolve and result in long-lasting sequelae, such as chronic neuropathy after platinum based therapy, are permitted to enroll
- Has received chemotherapy or radiotherapy within 14 days of first dose of study medication.
- Had a solid organ or hematologic transplant.

- Has experienced weight loss >10% over 2 months prior to first dose of study therapy.
- Has active autoimmune disease that has required systemic treatment in 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.
- Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy (at a dose greater than 10mg/day of Prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment.
- Has a diagnosed additional malignancy within 2 years prior to first dose of trial treatment with the exception of curatively treated basal cell carcinoma of the skin, squamous cell carcinoma of the skin or curatively resected in situ breast cancers. Subjects with another malignancy diagnosed >2 years prior to the first dose of trial medication who were treated with curative intent and are not undergoing active therapy will be eligible.
- Has a known history of, or any evidence of, interstitial lung disease or active non- infectious pneumonitis.
- Has an active infection requiring systemic therapy.
- Has clinically relevant ascites at baseline (defined as requiring paracentesis) or with moderate radiographic ascites. A minimal amount of radiographic ascites is allowed.
- Has a history of current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating investigator, including dialysis.
- Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.
- Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the screening visit through 120 days after the last dose of trial treatment.
- Has received prior therapy with anti–PD-1, anti–PD-L1, or anti–PD-L2 agents, or if the subject has previously participated in Merck pembrolizumab clinical trials.
- Has a known history of human immunodeficiency virus (HIV) (HIV 1/2 antibodies).
- Has known chronic or acute Hepatitis B (e.g., HBsAg reactive) or Hepatitis C infection (e.g., HCV RNA [qualitative] is detected).
- Note: To qualify for enrollment, antiviral therapy for HBV must be given for at least 3 months, and HBV viral load must be less than 100 IU/mL prior to first dose of study

  drug. Those on active HBV therapy with viral loads under 100 IU/mL should stay on

the same therapy throughout trial treatment. Those subjects who are anti-HBc (+), and negative for HBsAg, and negative for anti-HBs, and have an HBV viral load under 100 IU/mL do not require HBV anti-viral prophylaxis, but need close monitoring.

- Has dual infection with HBV/HCV or other hepatitis combinations at study entry.
- Has received a live vaccine within 30 days of planned start of study therapy (Cycle 1, Day 1).
- Note: The killed virus vaccines used for seasonal influenza vaccines for injection are allowed; however intranasal influenza vaccines (e.g., FluMist®) are live attenuated vaccines and are not allowed.

6.3. Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial.

Table 2. Inclusion of Women and Minorities

Accrual Targets					
Ethnic Category	**Sex/Gender**				
	Females		**Males**		**Total**
Hispanic or Latino	4	+	4	=	8
Not Hispanic or Latino	11	+	12	=	23
Ethnic Category: Total of all subjects	15	+	16	=	31
Racial Category					
Asian	2	+	2	=	4
Black or African American	2	+	2	=	4
White	11	+	12	=	23
Racial Category: Total of all subjects	15	+	16	=	31

6.4. Subject Recruitment

This study will be conducted at Columbia University Medical Center. Thirty-one patients will be needed to meet the primary study endpoint. . The amount of time required to complete this trial will depend on the rapidity of accrual. We estimate evaluation of 3-5 subjects a month in our center with enrollment of 2 subjects a month to complete accrual over 16-18 months with an anticipated 4-6 week pause after enrolling the 6^{th} subject for safety analysis. If the first dose level is deemed intolerable (≥ 2 DLTs), we will accrue 6 subjects at a lower dose level and complete 31 subjects (25 additional) at that dose level. Thus the maximum number of subjects enrolled in this study will be 37.

Participation is voluntary. The patient must be aware of the neoplastic nature of his/her disease and willingly consent after being informed of the procedures to be followed, the

experimental nature of the therapy, alternatives, potential benefits, side effects, risks, and discomforts. The investigator will make certain that an appropriate informed consent process is in place to ensure that potential research subjects, or their authorized representatives, are fully informed about the nature and objectives of the clinical study, the potential risks and benefits of study participation and their rights as research subjects.

6.5. Early Withdrawal of Subjects

When a subject discontinues/withdraws prior to trial completion, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 10.6 - Assessing and Recording Adverse Events. Subjects who discontinue for toxicity but do not withdraw consent from the study will continue to be followed for post-study treatment and survival as described. Subjects who a) attain a CR or b) complete 24 months of treatment with pembrolizumab may discontinue treatment with the option of restarting treatment in the future after consultation with the sponsor. After discontinuing treatment following assessment of CR, these subjects should return to the site for a Safety Follow-up Visit (described in Section 6.6.1 and then proceed to the Follow-Up Period of the study (described in Section 6.6.2).

6.5.1 When and How to Withdraw Subjects

Subjects may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn by the investigator or the Sponsor if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons.

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

- The subject or legal representative withdraws consent.
- Confirmed radiographic disease progression
    - *Note*: A subject may be granted an exception to continue on treatment with confirmed radiographic progression if clinically stable or clinically improved.
- Unacceptable adverse experiences
- Intercurrent illness that prevents further administration of treatment
- Investigator's decision to withdraw the subject
- The subject has a confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements
- The subject is lost to follow-up
- Completed 24 months of uninterrupted treatment with pembrolizumab or 35 administrations of study medication, whichever is later.
    - Note: 24 months of study medication is calculated from the date of first dose. Subjects who stop pembrolizumab after 24 months may be eligible for up to one year of additional study treatment if they progress after stopping study treatment after consultation with the sponsor.

- Administrative reasons

6.5.2 Data Collection and Follow-up for Withdrawn Subjects

The End of Treatment and Follow-up visit procedures are listed in Section 12.1 (Trial Flow Chart) and Section 12.3 (Administrative Procedures). After the end of treatment, each subject will be followed for 30 days for adverse event monitoring (serious adverse events will be collected for 90 days after the end of treatment as described in Section 10). Subjects who discontinue for reasons other than progressive disease will have post-treatment follow-up for disease status until disease progression, initiating a non-study cancer treatment, withdrawing consent or becoming lost to follow-up. After documented disease progression each subject will be followed by telephone for overall survival until death, withdrawal of consent, or the end of the study, whichever occurs first.

6.6. Post-Treatment Visits

6.6.1 Safety Follow-Up Visits

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

All AEs that occur prior to the Safety Follow-Up Visit should be recorded. Subjects with an AE of Grade >1 will be followed until the resolution of the AE to Grade 0-1 or until the beginning of a new anti-cancer therapy, whichever occurs first. SAEs that occur within 90 days of the end of treatment or before initiation of a new anti-cancer treatment should also be followed and recorded.

Subjects who are eligible for retreatment with pembrolizumab may have up to two safety follow- up visits, one after the Initial Treatment Period and one after the Second Course Treatment Phase.

6.6.2 Follow-Up Visits

Subjects who discontinue trial treatment for reasons other than disease progression will move into the Follow-up Phase and should be assessed Q8W by radiologic imaging to monitor disease status. Every effort should be made to collect information regarding disease status until the start of a new anti-cancer therapy, disease progression, death, or the end of the study.

Information regarding post-study anti-cancer treatment will be collected if new treatment is initiated.

6.6.3 Survival Follow-Up

Subjects, who experience disease progression (by site assessment) or start a new anti – cancer therapy, will move into the Survival Follow-Up Phase. Subjects should be contacted (e.g., by telephone or visit) every 12 weeks to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first Post-study anti-cancer therapy will be collected during survival follow-up.

7. REGISTRATION PROCEDURES

7.1. CUMC Research Participant Registration

Confirm eligibility as defined in the section entitled Criteria for Subject Eligibility.

Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures, along with applicable institutional policies and federal regulations.

Only Investigators/Research personnel properly trained and delegated to consent subjects for this protocol will participate in the consenting process. Furthermore, properly delegated/trained Physician Investigators (e.g., MD, MD PhD) are required to sign/verify a protocol specific Eligibility Checklist for each subject enrolled on the study, in addition to providing the relevant source documentation confirmation subject eligibility.

All participants must be centrally registered through the Central Registration Office within Herbert Irving Comprehensive Cancer Center at CUMC prior to initiation of study treatment. Registration hours are available Monday through Friday from 9:00am – 5:00pm EST (excluding holidays and weekends). Same day patient registrations (and after hour registrations) will be accommodated on a case by case basis provided that the study team has expressed all time sensitive registration concerns/cases in a timely manner to the Central Registration Office.

CPDM Central Registration Procedures:

Within 48 hours of obtaining consent (excluding holidays and weekends), a completed/signed IRB approved informed consent HIPAA form, and demographics forms must be submitted to the CPDM Central Registration Office via an email to CPDMRegistration@cumc.columbia.edu or fax to 212.305.5292, with the subject line "*AAAxxxxx* Pending Subject Registration Request (PHI)".
Upon receipt, applicable subject information as well as a "pending eligibility" status will be entered into HICCC's institutional database. This status will remain until further source documentation is made available to confirm overall patient eligibility. Required materials for all pending registration submissions are as follows:

- Completed/signed IRB approved/stamped Informed Consent Forms, including additional study ICFs (e.g., tissue, DNA, etc.), as applicable.
- The completed/signed IRB approved HIPAA Authorization form
- Completed/signed CPDM ICF checklist
- Completed/signed HICCC personal census form
- Completed/signed CPDM Demographics Note to File

In order to confirm eligibility status, Investigators/designees (e.g., study specific Clinical Research Coordinator/Research Nurse, etc.) must submit the following documentation to the

Central Registration Office via email or fax:

- The completed/signed study specific Eligibility Checklist (signed by an Physician level Investigator)

- Copies of source documentation necessary for each item to be verified on the CPDM specific Eligibility Checklist, including but not limited to:
    - Copy of required laboratory test and procedure reports (e.g., hematology, serum chemistry, pregnancy test when applicable, MRI reports, CT/bone scans, etc.)
    - Copy of pathology and surgical reports
    - Copy of clinic note(s) or other appropriate medical records capturing the consent process information, along with providing source documentation of any other items needed for screening/eligibility that are not captured in other source document forms (e.g., positive investigator statements of unique eligibility items not captured via other direct source documentation, concomitant medication lists, etc.)
    - Protocol deviation/waiver approvals (if applicable)
- **Please note**: subject line of email or fax should include the following: "*AAAR3554* Complete Subject Registration Request (PHI)".

Upon receipt of the above mentioned documentation, participant eligibility information will be verified by a qualified Central Registration Registrar. If any questions arise during the review process, queries in the form of emails will be addressed to the applicable study team personnel for clarification prior to enrollment. All applicable finalized registration/eligibility information will then be entered into HICCC's institutional CTMS database by the Central Registration Registrar. Upon completion, an official subject registration notification email will be sent to the PI/research team which will include eligibility/enrollment status, as well as subject ID information. Protocol therapy may not be initiated prior to receipt of this notification from the Central Registration Office.

All screen fail/ineligible subjects, as well as subject's who withdraw consent prior to enrollment/initiation of protocol therapy must be submitted to the Central Registration office in a manner analogous to the procedures noted above. Applicable source documentation will be required within the corresponding submissions.

8. TREATMENT PLAN

8.1. Agent Administration

Treatment will be administered on an outpatient basis. Reported adverse events and potential risks for Pembrolizumab and Azacitidine are described in Section 10. There are no

dose modifications for Pembrolizumab. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy. The treatment to be used in this trial is outline below in Table 3.

Table 3 Trial Treatment Schedule

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen	Use
Pembrolizumab	200 mg	Q3W	IV Infusion	Dosed every 21 days beginning in week 3 of study.	Experimental
Azacitidine	50 mg/m^2	Q4W	SubQ	Day 1 to 5 of on a 28-day cycle	Experimental

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

8.2. Dose Selection/Modification

8.2.1 Dose Selection

The rationale for selection of doses to be used in this trial is provided in Section 4 Background and Rationale.

Details on preparation and administration of pembrolizumab (MK-3475) are provided in the Pharmacy manual. Preparation and administration of azacitidine should be completed as per the approved product label. See Section 8.1 for general recommendations for administration.

Body surface area (BSA) in m^2 should be calculated per local guidance.

8.2.2 Dose Modification (Escalation/Titration/Other)

The Common Terminology Criteria for Adverse Events version 4.0 (CTCAE 4.0) must be used to grade the severity of adverse events.

If appropriate, the investigators may attribute each toxicity event to either one of the investigational agents and use stepwise dose modifications according to Table 5. Pembrolizumab dose reductions are not permitted. Pembrolizumab treatment may be interrupted or discontinued due to toxicity.

If a dose level reduction for toxicity occurs with azacitidine, the dose may not be re-escalated. Dose modifications are always based on the previous cycle.

Subjects may have up to 1 dose level reductions of azacitidine as described in Table 6. If further toxicity occurs or the criteria for resuming treatment are not met, the subject must be discontinued from treatment.

If a toxicity is not otherwise specified, investigators should refer to the label or local standard of care for dose adjustments. At the investigator's discretion, dose modification according to Table 5 is allowed for intolerable Grade 2-3 toxicities that are not specified in the tables below.

8.3. Pembrolizumab

8.2.3 General Concomitant Medication and Supportive Care Guidelines

8.2.4 Concomitant Medications/Vaccinations (allowed & prohibited)

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

8.2.5 Acceptable Concomitant Medications

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

All concomitant medications received within 28 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered after 30 days after the last dose of trial treatment should be recorded for SAEs and ECIs as defined in Section 10.

8.2.6 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 PI.

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

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

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

8.2.7 Rescue Medications

No rescue medications are specified to be used in this trial.

8.2.8 Supportive Care Guidelines

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of adverse events with potential immunologic etiology are outlined below. Toxicities associated or possibly associated with pembrolizumab should be managed according to standard medical practice. Additional tests, such as autoimmune serology or biopsies, should be used to evaluate for a possible immunogenic etiology. Attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care.

Although most immune-related adverse events observed with immunomodulatory agents have been mild and self-limiting, such events should be recognized early and treated promptly to avoid potential major complications. Discontinuation of pembrolizumab may not have an immediate therapeutic effect, and in severe cases, immune-related toxicities may require acute management with topical steroids, systemic corticosteroids, or other immunosuppressive agents. The treatment guidelines are intended to be applied when the investigator determines the events to be related to trial treatment.

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

MANAGEMENT GUIDELINES

- **Immune-related hepatitis**

  Immune-related hepatitis has been associated with the administration of pembrolizumab. Patients with right upper quadrant pain and/or unexplained nausea or vomiting should have liver function tests (LFTs) performed immediately and reviewed before administration of the next dose of study drug.

For patients with elevated LFTs, concurrent medication, viral hepatitis, biliary obstruction, and toxic or neoplastic etiologies should be considered and addressed, as appropriate.

- For **Grade 1 events**, continue pembrolizumab and monitor LFTs until values resolve to within normal limits or to baseline values.

- For **Grade 2 events of >5 days' duration**:
  - Withhold pembrolizumab for up to 12 weeks after event onset. Pembrolizumab may be withheld for a longer period of time (i.e. >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of 10 mg/day or less of oral prednisone. The acceptable length of the extended period of time will be determined by the investigator.
  - Initiate treatment with systemic corticosteroids equivalent to 1-2 mg/kg/day oral prednisone.
  - Monitor liver function tests more frequently until returned to baseline values (consider weekly).
  - If event resolves to Grade 1 or less, resume pembrolizumab. If corticosteroids have been initiated, they must be tapered over no less than 4 weeks to the equivalent of 10 mg/day oral prednisone or less before pembrolizumab may be resumed.

- For **Grade 3-4 events**:
  - Permanently discontinue pembrolizumab.
  - Consider referral to gastrointestinal specialist for evaluation and liver biopsy to establish etiology of hepatic injury.
  - Initiate treatment with systemic corticosteroids equivalent to 1-2 mg/kg/day oral prednisone.
  - If the event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.
  - If event resolves to Grade 1 or better, taper corticosteroids over no less than 4 weeks.

- **Immune-related pneumonitis**

  Dyspnea, cough, fatigue, hypoxia, pneumonitis, and pulmonary infiltrates have been associated with the administration of pembrolizumab. Patients will be assessed for pulmonary signs and symptoms throughout the study and will have computed tomography (CT) scans of the chest performed at every tumor assessment.

  All pulmonary events should be thoroughly evaluated for other commonly reported etiologies such as pneumonia or other infection, lymphangitic carcinomatosis,

pulmonary embolism, heart failure, chronic obstructive pulmonary disease, or pulmonary hypertension.

Management guidelines for pulmonary events, including pneumonitis:

- For **Grade 1 events**, continue pembrolizumab and monitor closely. Re-evaluate on serial imaging and consider referral to a pulmonary specialist.

- For **Grade 2 events**:
  - Withhold pembrolizumab for up to 12 weeks after event onset. Pembrolizumab may be withheld for a longer period of time (i.e. >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of 10 mg/day or less of oral prednisone.
  - Initiate treatment with systemic corticosteroids equivalent to 1-2 mg/kg/day oral prednisone.
  - Refer patient to pulmonary specialist and consider bronchoscopic alveolar lavage.
  - When symptoms improve to Grade 1 or less, resume pembrolizumab. Steroid taper should be started and continued over no less than 4 weeks.

- For **Grade 3-4 events**:
  - Permanently discontinue pembrolizumab.
  - Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day oral prednisone.
  - If the event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.
  - If event resolves to Grade 1 or better, taper corticosteroids over no less than 4 weeks.

- Add prophylactic antibiotics for opportunistic infections in the case of prolonged steroid administration.

- **Immune-related colitis**

  Subjects should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stools, with or without fever) and of bowel perforation (such as peritoneal signs and ileus).

  All events of diarrhea or colitis should be thoroughly evaluated for other more common etiologies. For events of significant duration or magnitude or associated with signs of systemic inflammation or acute-phase reactants (e.g. increased C-reactive protein, platelet count, or bandemia): Perform sigmoidoscopy (or colonoscopy, if appropriate) with colonic biopsy, with three to five specimens for standard paraffin block to check

for inflammation and lymphocytic infiltrates to confirm colitis diagnosis.

- 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 1 diarrhea or colitis**, continue pembrolizumab. If symptoms persist >7 days, endoscopy is recommended.

- For **Grade 2 diarrhea or colitis**:
  - Withhold pembrolizumab for up to 12 weeks after event onset. Pembrolizumab may be withheld for a longer period of time (i.e. >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of 10 mg/day or less of oral prednisone.
  - Refer to GI specialist for evaluation and confirmatory biopsy.
  - For recurrent events or events that persist >5 days, initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day oral prednisone.
  - If symptoms improve to Grade 1 or less, resume pembrolizumab. If corticosteroids have been initiated, they must be tapered over no less than 4 weeks to the equivalent of 10 mg/day oral prednisone or less before pembrolizumab may be resumed.

- For **Grade 3 diarrhea or colitis**:
  - Withhold pembrolizumab for up to 12 weeks after event onset. Pembrolizumab may be withheld for a longer period of time (i.e. >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of 10 mg/day or less of oral prednisone.
  - Refer to GI specialist for evaluation and confirmatory biopsy.
  - Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day IV methylprednisolone and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement.
  - If symptoms improve to Grade 1 or less, resume pembrolizumab. If corticosteroids have been initiated, they must be tapered over no less than 4 weeks to the equivalent of 10 mg/day oral prednisone or less before pembrolizumab may be resumed.

- For **Grade 4 diarrhea or colitis**:
  - Permanently discontinue pembrolizumab.
  - Refer to GI specialist for evaluation and confirmatory biopsy.
  - Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day IV methylprednisolone and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement.
  - If the event does not improve within 48 hours after initiating corticosteroids,

consider adding an immunosuppressive agent.
    - If the event resolves to Grade 1 or better, taper corticosteroids over no less than 4 weeks.

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

    - **For new onset T1DM** or **Grade 3-4 Hyperglycemia**
        - Withhold pembrolizumab
        - Insulin replacement therapy is recommended for T1DM and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria.
        - Monitor for glucose control.
        - Evaluate patients with plasma glucose and a metabolic panel, urine ketones, HbA1c, and C-peptide.
        - Resume pembrolizumab when symptoms resolve and glucose levels are stable.

- **Immune-related hypophysitis**
  Patients with unexplained symptoms such as headache, fatigue, myalgias, impotence, constipation, or mental status change should be investigated for the presence of thyroid, pituitary, or adrenal endocrinopathies. The patient should be referred to an endocrinologist if an endocrinopathy is suspected. Thyroid-stimulating hormone (TSH) and free triiodothyronine and thyroxine levels should be measured to determine whether thyroid abnormalities are present. Pituitary hormone levels and function tests (e.g. TSH, growth hormone, luteinizing hormone, follicle-stimulating hormone, testosterone, prolactin, adrenocorticotropic hormone [ACTH] levels, and ACTH stimulation test) and magnetic resonance imaging (MRI) of the brain (with detailed pituitary sections) may help to differentiate primary pituitary insufficiency from primary adrenal insufficiency.

    - For **Grade 2 or 3 events**:
        - Withhold pembrolizumab for up to 12 weeks after event onset. Pembrolizumab may be withheld for a longer period of time (i.e. >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of 10 mg/day or less of oral prednisone.
        - Refer patient to endocrinologist.
        - Perform brain MRI (pituitary protocol).
        - Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day IV methylprednisolone and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement.
        - Initiate hormone replacement if clinically indicated.

- If symptoms improve to Grade 1 or less, resume pembrolizumab. If corticosteroids have been initiated, they must be tapered over no less than 4 weeks to the equivalent of 10 mg/day oral prednisone or less before pembrolizumab may be resumed.
- For recurrent hypophysitis, treat as Grade 4 event.

- For **Grade 4 event**:
  - Permanently discontinue pembrolizumab.
  - Refer patient to endocrinologist.
  - Perform brain MRI (pituitary protocol).
  - Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day IV methylprednisolone and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement.
  - Initiate hormone replacement if clinically indicated.

- **Immune-related hyperthyroidism or hypothyroidism**

  Patients with unexplained symptoms such as headache, fatigue, myalgias, impotence, constipation, or mental status change should be investigated for the presence of thyroid, pituitary, or adrenal endocrinopathies. The patient should be referred to an endocrinologist if an endocrinopathy is suspected. Thyroid-stimulating hormone (TSH) and free triiodothyronine and thyroxine levels should be measured to determine whether thyroid abnormalities are present. Pituitary hormone levels and function tests (e.g. TSH, growth hormone, luteinizing hormone, follicle-stimulating hormone, testosterone, prolactin, adrenocorticotropic hormone [ACTH] levels, and ACTH stimulation test) and magnetic resonance imaging (MRI) of the brain (with detailed pituitary sections) may help to differentiate primary pituitary insufficiency from primary adrenal insufficiency.

  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.

  - **Asymptomatic hypothyroidism**:
    - Continue pembrolizumab
    - Initiate treatment with thyroid replacement hormone per standard of care

  - **Symptomatic hypothyroidism**:
    - Withhold pembrolizumab
    - Initiate treatment with thyroid replacement hormone per standard of care
    - Consider referral to endocrinology

        - Resume pembrolizumab when symptoms are controlled and thyroid function is normal.

    - **Asymptomatic hyperthyroidism**:
        - TSH ≥ 0.1 mU/L and < 0.5 mU/L
            - Continue pembrolizumab
            - Monitor TSH every 4 weeks
        - TSH <0.1 mU/L:
            - Follow guidelines for symptomatic hyperthyroidism.

    - **Symptomatic hyperthyroidism**:
        - Withhold pembrolizumab
        - Initiate treatment with anti-thyroid drug such as methimazole or carbimazole as needed
        - Consider referral to endocrinology
        - Resume pembrolizumab when symptoms are controlled and thyroid function is normal.

- **Immune-related adrenal insufficiency**

  Patients with unexplained symptoms such as headache, fatigue, myalgias, impotence, constipation, or mental status change should be investigated for the presence of thyroid, pituitary, or adrenal endocrinopathies. The patient should be referred to an endocrinologist if an endocrinopathy is suspected. Thyroid-stimulating hormone (TSH) and free triiodothyronine and thyroxine levels should be measured to determine whether thyroid abnormalities are present. Pituitary hormone levels and function tests (e.g. TSH, growth hormone, luteinizing hormone, follicle-stimulating hormone, testosterone, prolactin, adrenocorticotropic hormone [ACTH] levels, and ACTH stimulation test) and magnetic resonance imaging (MRI) of the brain (with detailed pituitary sections) may help to differentiate primary pituitary insufficiency from primary adrenal insufficiency.

    - **Symptomatic adrenal insufficiency, Grade 2-4**:
        - Withhold pembrolizumab for up to 12 weeks after event onset. Pembrolizumab may be withheld for a longer period of time (i.e. >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of 10 mg/day or less of oral prednisone.
        - Refer patient to endocrinologist.
        - Perform appropriate imaging.
        - Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day IV methylprednisolone and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement.
        - If event resolves to Grade 1 or better and patient is stable on replacement therapy, resume pembrolizumab. If corticosteroids have been initiated, they must be tapered over no less than 4 weeks to the

equivalent of 10 mg/day oral prednisone or less before pembrolizumab may be resumed.

- **Immune-mediated nephritis**

  Patients with abnormal renal function should be evaluated and treated for other more common etiologies (including prerenal and postrenal causes, and concomitant medications such as non-steroidal anti-inflammatory drugs). Refer the patient to a renal specialist if clinically indicated. A renal biopsy may be required to enable a definitive diagnosis and appropriate treatment.

  - For **Grade 1** events: Continue pembrolizumab and monitor kidney function closely until values resolve to within normal limits or to baseline values.

  - **Grade 2** events:
    - Withhold pembrolizumab for up to 12 weeks after event onset. Pembrolizumab may be withheld for a longer period of time (i.e. >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of 10 mg/day or less of oral prednisone.
    - Refer patient to a renal specialist.
    - Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day oral prednisone.
    - If event resolves to Grade 1 or better and patient is stable on replacement therapy, resume pembrolizumab. If corticosteroids have been initiated, they must be tapered over no less than 4 weeks to the equivalent of 10 mg/day oral prednisone or less before pembrolizumab may be resumed.

  - For **Grade 3 or 4** events:
    - Permanently discontinue pembrolizumab.
    - Refer patient to a renal specialist.
    - Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day oral prednisone.
    - If the event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.
    - If event resolves to Grade 1 or better, taper corticosteroids over no less than 4 weeks.

- **Immune-mediated dermatologic events**

  The majority of rashes are mild and self-limited, with or without pruritus. A dermatologist should evaluate persistent and/or severe rash or pruritus. A biopsy should be considered unless contraindicated.

  - **Grade 1**:
    - Continue pembrolizumab.

        - Consider treatment with topical corticosteroids and/or other symptomatic therapy (e.g., antihistamines).

    - **Grade 2**:
        - Continue pembrolizumab.
        - Consider patient referral to a dermatologist.
        - Initiate treatment with topical corticosteroids.
        - Consider treatment with higher-potency topical corticosteroids if event does not improve.

    - **Grade 3**:
        - Withhold pembrolizumab for up to 12 weeks after event onset. Pembrolizumab may be withheld for a longer period of time (i.e. >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of 10 mg/day or less of oral prednisone.
        - Refer patient to a dermatologist.
        - Initiate treatment with corticosteroids equivalent to 10 mg/day oral prednisone, increasing dose to 1-2 mg/kg/day if event does not improve within 48-72 hours.
        - If event resolves to Grade 1 or better and patient is stable on replacement therapy, resume pembrolizumab. If corticosteroids have been initiated, they must be tapered over no less than 4 weeks to the equivalent of 10 mg/day oral prednisone or less before pembrolizumab may be resumed.

    - **Grade 4**:
        - Permanently discontinue pembrolizumab.

- **Immune-mediated ocular events**
  An ophthalmologist should evaluate visual complaints (e.g. uveitis, retinal events).

    - **Grade 1**:
        - Continue pembrolizumab.
        - Referral to an ophthalmologist is strongly recommended.
        - Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy.
        - If symptoms persist, treat as a Grade 2 event.

    - **Grade 2**:
        - Withhold pembrolizumab for up to 12 weeks after event onset. Pembrolizumab may be withheld for a longer period of time (i.e. >12 weeks after event onset) to allow for corticosteroids (if initiated) to be

reduced to the equivalent of 10 mg/day or less of oral prednisone.
- Referral to an ophthalmologist is strongly recommended.
- Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy.
- If event resolves to Grade 1 or better and patient is stable on replacement therapy, resume pembrolizumab. If corticosteroids have been initiated, they must be tapered over no less than 4 weeks to the equivalent of 10 mg/day oral prednisone or less before pembrolizumab may be resumed.

- **Grade 3 or 4**:
  - Permanently discontinue pembrolizumab.
  - Refer patient to an ophthalmologist.
  - Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day oral prednisone.
  - If event resolves to Grade 1 or better, taper corticosteroids over no less than 4 weeks.

- **Immune-related pancreatitis**

  Symptoms of abdominal pain associated with elevations of amylase and lipase, suggestive of pancreatitis, have been associated with the administration of pembrolizumab. The differential diagnosis of acute abdominal pain should include pancreatitis. Appropriate work up should include an evaluation for ductal obstruction, as well as serum amylase and lipase tests.

  - **Amylase and/or lipase elevation, Grade 2**:
    - **Amylase and/or lipase >1.5-2.0x ULN**
      - Continue pembrolizumab
      - Monitor amylase and lipase weekly
      - For prolonged elevation (e.g., >3 weeks), consider treatment with corticosteroids equivalent to 10 mg/day oral prednisone.
    - **Asymptomatic with amylase and/or lipase >2.0-5.0x ULN**
      - Treat as a Grade 3 event

  - **Amylase and/or lipase elevation, Grade 3 or 4**:
    - Withhold pembrolizumab for up to 12 weeks after event onset. Pembrolizumab may be withheld for a longer period of time (i.e. >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of 10 mg/day or less of oral prednisone.
    - Refer patient to a GI specialist.
    - Monitor amylase and lipase every other day.
    - If no improvement, consider treatment with corticosteroids equivalent

to 1-2 mg/kg/day oral prednisone.
- If event resolves to Grade 1 or better and patient is stable on replacement therapy, resume pembrolizumab. If corticosteroids have been initiated, they must be tapered over no less than 4 weeks to the equivalent of 10 mg/day oral prednisone or less before pembrolizumab may be resumed.
- For recurrent events, permanently discontinue pembrolizumab.

- **Immune-related pancreatitis, Grade 2 or 3**:
  - Withhold pembrolizumab for up to 12 weeks after event onset. Pembrolizumab may be withheld for a longer period of time (i.e. >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of 10 mg/day or less of oral prednisone.
  - Refer patient to a GI specialist.
  - Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day IV methylprednisolone and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement.
  - If event resolves to Grade 1 or better and patient is stable on replacement therapy, resume pembrolizumab. If corticosteroids have been initiated, they must be tapered over no less than 4 weeks to the equivalent of 10 mg/day oral prednisone or less before pembrolizumab may be resumed.
  - For recurrent events, permanently discontinue pembrolizumab.

- **Immune-related pancreatitis, Grade 4**:
  - Permanently discontinue pembrolizumab.
  - Refer patient to a GI specialist.
  - Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day IV methylprednisolone and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement.
  - If the event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.
  - If event resolves to Grade 1 or better, taper corticosteroids over no less than 4 weeks.

- **Immune-related myocarditis**

  Immune-related myocarditis should be suspected in any patient presenting with signs or symptoms suggestive of myocarditis, including, but not limited to dyspnea, chest pain, fatigue, decreased exercise tolerance, or syncope. Immune-related myocarditis needs to be distinguished from myocarditis resulting from infection (commonly viral, e.g., in a patient who reports a history of gastrointestinal illness), ischemic events, underlying arrhythmias, exacerbation of preexisting cardiac conditions, or progression of malignancy.

All patients with possible myocarditis should be urgently evaluated by performing cardiac enzyme assessment, an ECG, a chest X-ray, an echocardiogram, and a cardiac MRI as appropriate per institutional guidelines. A cardiologist should be consulted. An endomyocardial biopsy may be considered to enable a definitive diagnosis and appropriate treatment, if clinically indicated.

- For **Grade 2 events**:
  - Withhold pembrolizumab for up to 12 weeks after event onset. Pembrolizumab may be withheld for a longer period of time (i.e. >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of 10 mg/day or less of oral prednisone.
  - Refer patient to a cardiologist.
  - Initiate treatment as per institutional guidelines.
  - Consider treatment with corticosteroids equivalent to 1-2 mg/kg/day IV methylprednisolone and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement.
  - If event resolves to Grade 1 or better and patient is stable on replacement therapy, resume pembrolizumab. If corticosteroids have been initiated, they must be tapered over no less than 4 weeks to the equivalent of 10 mg/day oral prednisone or less before pembrolizumab may be resumed.

- For **Grade 3 or 4 events**:
  - Permanently discontinue pembrolizumab.
  - Refer patient to a cardiologist.
  - Initiate treatment as per institutional guidelines.
  - Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day IV methylprednisolone and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement.
  - If the event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.
  - If event resolves to Grade 1 or better, taper corticosteroids over no less than 4 weeks.

- **Immune-related neuropathies (i.e. myasthenic syndrome/myasthenia gravis, Guillain-Barre syndrome)**

  Patients may present with signs and symptoms of sensory and/or motor neuropathy. Diagnostic work up is essential for an accurate characterization to differentiate between alternative etiologies.

  - **Immune-related neuropathy, Grade 1**: Continue pembrolizumab and investigate etiology.

- **Immune-related neuropathy, Grade 2**:
  - Withhold pembrolizumab for up to 12 weeks after event onset. Pembrolizumab may be withheld for a longer period of time (i.e. >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of 10 mg/day or less of oral prednisone.
  - Investigate etiology.
  - Initiate treatment as per institutional guidelines.
  - If event resolves to Grade 1 or better and patient is stable on replacement therapy, resume pembrolizumab. If corticosteroids have been initiated, they must be tapered over no less than 4 weeks to the equivalent of 10 mg/day oral prednisone or less before pembrolizumab may be resumed.

- **Immune-related neuropathy, Grade 3 or 4**:
  - Permanently discontinue pembrolizumab.
  - Initiate treatment as per institutional guidelines.

- **Myasthenia gravis and Guillain-Barre syndrome (any grade)**:
  - Permanently discontinue pembrolizumab.
  - Refer patient to a neurologist.
  - Initiate treatment as per institutional guidelines.
  - Consider treatment with corticosteroids equivalent to 1-2 mg/kg/day oral or IV prednisone.

- **Immune-related meningoencephalitis**

  Immune-related meningoencephalitis should be suspected in any patient presenting with signs or symptoms suggestive of meningitis or encephalitis, including, but not limited to, headache, neck pain, confusion, seizure, motor or sensory dysfunction, and altered or depressed level of consciousness. Encephalopathy from metabolic or electrolyte imbalances needs to be distinguished from potential meningoencephalitis resulting from infection (bacterial, viral, or fungal) or progression of malignancy, or secondary to a paraneoplastic process.

  All patients being considered for meningoencephalitis should be urgently evaluated with a CT scan and/or MRI scan of the brain to evaluate for metastasis, inflammation, or edema. If deemed safe by the treating physician, a lumbar puncture should be performed and a neurologist should be consulted.

  Patients with signs and symptoms of meningoencephalitis, in the absence of an identified alternate etiology, should be treated according to the guidelines.

  - **Immune-related meningoencephalitis (all grades)**:

- Permanently discontinue pembrolizumab.
- Refer patient to a neurologist.
- Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day IV methylprednisolone and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement.
- If the event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.
- If event resolves to Grade 1 or better, taper corticosteroids over no less than 4 weeks.

- **Myositis**

  Myositis or inflammatory myopathies are a group of disorders sharing the common feature of inflammatory muscle injury; dermatomyositis and polymyositis are among the most common disorders. Initial diagnosis is based on clinical (muscle weakness, muscle pain, skin rash in dermatomyositis), biochemical (serum creatine kinase increase), and imaging (electromyography/MRI) features, and is confirmed with a muscle biopsy.

  - For **Grade 1** events: Continue pembrolizumab, refer patient to a rheumatologist or neurologist, and initiate treatment as per institutional guidelines.

  - For **Grade 2** events:
    - Withhold pembrolizumab for up to 12 weeks after event onset. Pembrolizumab may be withheld for a longer period of time (i.e. >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of 10 mg/day or less of oral prednisone.
    - Refer patient to a rheumatologist or neurologist.
    - Initiate treatment as per institutional guidelines.
    - Consider treatment with corticosteroids equivalent to 1-2 mg/kg/day IV methylprednisolone and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement.
    - If corticosteroids are initiated and the event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.
    - If event resolves to Grade 1 or better and patient is stable on replacement therapy, resume pembrolizumab. If corticosteroids have been initiated, they must be tapered over no less than 4 weeks to the equivalent of 10 mg/day oral prednisone or less before pembrolizumab may be resumed.

  - For **Grade 3** events:
    - Withhold pembrolizumab for up to 12 weeks after event onset.

Pembrolizumab may be withheld for a longer period of time (i.e. >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of 10 mg/day or less of oral prednisone.
- Refer patient to a rheumatologist or neurologist.
- Initiate treatment as per institutional guidelines. Respiratory support may be required in more severe cases.
- Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day IV methylprednisolone, or higher-dose bolus if patient is severely compromised (e.g., cardiac or respiratory symptoms, dysphagia, or weakness that severely limits mobility); convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement.
- If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.
- If event resolves to Grade 1 or better and patient is stable on replacement therapy, resume pembrolizumab. If corticosteroids have been initiated, they must be tapered over no less than 4 weeks to the equivalent of 10 mg/day oral prednisone or less before pembrolizumab may be resumed.
- For recurrent events, treat as a Grade 4 event.

- For **Grade 4** events:
  - Permanently discontinue pembrolizumab.
  - Refer patient to a rheumatologist or neurologist.
  - Initiate treatment as per institutional guidelines. Respiratory support may be required in more severe cases.
  - Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day IV methylprednisolone, or higher-dose bolus if patient is severely compromised (e.g., cardiac or respiratory symptoms, dysphagia, or weakness that severely limits mobility); convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement.
  - If the event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.
  - If event resolves to Grade 1 or better, taper corticosteroids over no less than 4 weeks.

- **Infusion-related reactions**

Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. No premedication is indicated for the administration of Cycle 1 of pembrolizumab. However, patients who experience an IRR with Cycle 1 of pembrolizumab may receive premedication with antihistamines or antipyretics/analgesics (e.g., acetaminophen) for subsequent infusions.

Table 4 Infusion Reaction Treatment Guidelines

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

8.4. Azacitidine

Azacitidine is supplied as a lyophilized powder in a single-dose vial. Each vial contains 100 mg of azacitidine. Azacitidine is administered at a dose of 50 mg/m^2 by SubQ injection, in rotating sites (thigh, abdomen, or upper arm) repeated for 5 consecutive business days. This cycle should be repeated after 4 weeks. Patients should be premediated with standard anti-emetic therapy.

Contraindications to the administration of azaciditine include advanced malignant hepatic tumors and hypersensitivity to azacitidine or mannitol. Patients with severe preexisting hepatic

impairment are at higher risk for toxicity. Azacitidine is primarily excreted by the kidneys. No formal drug interaction studies with azacitidine have been conducted. Whether azacitidine metabolism may be affected by known microsomal enzyme inhibitors or inducers in the liver has not yet been studied. *In vitro* studies have shown that azacitidine does not cause inhibition of CYP2B6 and CYP2C8 but the potential of azacitidine to inhibit other cytochrome P450 enzymes is not known. Other *in vitro* studies indicate that azacitidine does not induce CYP 1A2, 2C19, or 3A4/5.

8.5. Diet/Activity/Other Considerations

8.2.9 Diet

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

8.2.10 Contraception

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

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

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

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

- OR

- OR

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

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

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

(1) practice abstinence* from heterosexual activity;

- OR

(2) use (or have their partner use) acceptable contraception during heterosexual activity. Acceptable methods of contraception are**:

- Single method (one of the following is acceptable):
  - intrauterine device (IUD)
  - vasectomy of a female subject's sole male partner
  - contraceptive rod implanted into the skin
- Combination method (requires use of two of the following):
  - diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide)
  - cervical cap with spermicide (nulliparous women only)
  - contraceptive sponge (nulliparous women only)
  - male condom or female condom (cannot be used together)
  - hormonal contraceptive: oral contraceptive pill (estrogen/progestin pill or progestin- only pill), contraceptive skin patch, vaginal contraceptive ring, or subcutaneous contraceptive injection

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

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

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study, subjects of childbearing potential must adhere to the contraception requirement (described above) from the day of study medication initiation (or 14 days prior to the initiation of trial treatment [Cycle 1 Day 1] for oral contraception) throughout the study period up to 120 days after the last dose of trial therapy. If there is any question that a subject of childbearing potential will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

8.2.11 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-Investigator and to Merck without delay and within 24 hours to the Sponsor-Investigator 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-Investigator.

8.2.12 Use in Nursing

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.

8.6. Duration of Therapy

In the absence of treatment delays due to adverse events, treatment may continue for up to 2 years (35 cycles of pembrolizumab) or until one of the following criteria applies:

- Disease progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse events(s)
- Patient decides to withdraw from the study
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator

8.7. Duration of Follow Up

Patients will be followed for 4 weeks after completion or removal from study or until death, whichever occurs first. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event..

8.8. Criteria for Removal from Study

Patients will be removed from study when any of the criteria listed in Section 6.5.1 applies. The reason for study removal and the date the patient was removed will be documented in the Case Report Form.

9. DOSING DELAYS/DOSE MODIFICATIONS

9.1. Dose Modification for Pembrolizumab

Adverse events (both non-serious and serious) associated with pembrolizumab exposure may represent an immunologic etiology. These adverse events may occur shortly after the first dose or several months after the last dose of treatment. Pembrolizumab must be withheld for drug- related toxicities and

severe or life-threatening AEs as per Table 5 below. See Section 8.3.6 for supportive care guidelines, including use of corticosteroids.

Table 5 Dose Modification Guidelines for Pembrolizumab-Related Adverse Events

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

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

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

[b] If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose; Refer to Table 4– Infusion Treatment Guidelines for further management details.

[c] For grade 2 pneumonitis, should this recur, pembrolizumab should be discontinued.

[d] 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.

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

9.2 Dose Modification for Azacitidine

If myelosuppression is present, subsequent treatment cycles of azacitidine should be delayed until there is hematologic recover (ANC ≥ 1,000/μL, platelets ≥ 50,000/μL). Following the first cycle of azacitidine treatment, if any of the following non-hematologic toxicities are present, azacitidine treatment should not be restarted until the toxicity is resolved: 1) serum bicarbonate level < 20 mEq/L, 2) serum creatinine ≥ 2 mg/dL; 3) SGPT, total bilirubin ≥ 2 times ULN; 4)
and active or uncontrolled infection. Subjects will continue taking pembrolizumab on schedule if toxicity is not related to this agent.

Table 6 Dose Levels for Trial Medications

Drug	Starting Dose	Dose Level -1	Dose Level -2
Pembrolizumab	200 mg fixed dose	No dose reductions are permitted	No dose reductions are permitted
Azacitidine	50 mg/m2	40 mg/m2	Discontinue

10. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

10.1. Definition of an Overdose for this Protocol and Reporting of Overdose to Sponsor-Investigator and to Merck

For purposes of this trial, an overdose of:

- pembrolizumab will be defined as any dose of 1,000 mg or greater (≥5 times the indicated dose).
- Azacitidine will be defined as any dose >/= 20% over the prescribed dose.

No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

There is no known specific antidote for azacitidine overdosage. In the event of an overdose of azacitidine, the patient will be monitored with appropriate blood counts and will receive supportive treatment as necessary..

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

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

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

10.2. Anticipated Adverse Events

Pembrolizumab: Refer to section 8.3.6 for specific adverse events related to pembrolizumab.

Azacitidine: The primary toxicities of azacitidine include bone marrow suppression, nausea and vomiting, diarrhea, constipation, injection site erythema, pyrexia, and ecchymosis.

10.3. Adverse Events Definitions:

10.2.1 Adverse Event:

An adverse event (AE) is any untoward or unfavorable medical occurrence in a human subject, including abnormal sign, symptom or disease, temporally associated with the subject's participation in research, whether or not considered related to the subject's participation in the research. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

10.2.2 Serious Adverse Event:

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

- fatal
- life-threatening
- requires inpatient hospitalization/prolongation of existing hospitalization, unless:
    - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (procedures such as central line placements, paracentesis, pain control)
    - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of study drug
    - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of an SAE given above/below and not resulting in hospital

admissions
    - social reasons and respite care in the absence of any deterioration in the patient's general condition
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious events should be regarded as non-serious adverse events.

Progression of the cancer under study is not considered an adverse event.

10.2.3 Unanticipated Problem:

An unanticipated problem is any incident, experience or outcome involving risks to subjects or others in any human subjects research that meets all of the following criteria:

- Unexpected (in terms of nature, severity or frequency) given (a) the research procedures that are described in the IRB-approval protocol and informed consent document, and (b) the characteristics of the subject population being studied;
- Related or possibly related to participation in such research (e.g., there is a reasonable possibility that the incident, experience or outcome may have been caused by the procedures involved in such research); and
- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic or social harm) than was previously known or recognized.

10.4. Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be reported within 24 hours to the Sponsor-Investigator and within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220).

For the time period beginning when the consent form is signed until treatment allocation/randomization, any ECI, or follow up to an ECI, that occurs to any subject must be reported within 24 hours to the Sponsor-Investigator and within 2 working days to Merck Global Safety if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new

anticancer therapy, whichever is earlier, any ECI, or follow up to an ECI, whether or not related to Merck product, must be reported within 24 hours to the Sponsor and within 24 hours to Merck Global Safety.

Events of clinical interest for this trial include:

- An overdose of Merck product, as defined in Section 10.1 - Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor-Investigator, that is not associated with clinical symptoms or abnormal laboratory results.
- An elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

- *Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology.

10.5. Adverse Event Reporting Period

The study period during which adverse events must be reported is normally defined as the period from the initiation of any study procedures (e.g., after the first dose of study treatment) to the end of the study treatment (e.g., last dose of study treatment) and/or follow-up. For this study, the study treatment follow-up is defined as 30 days following the last administration of study treatment, or 30 days following the decision to remove the subject from study treatment, whichever is earliest.

10.2.4 Baseline/Preexisting Condition

A baseline/preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or if the character of the condition worsens during the study period.

10.2.5 General Physical Examination Findings

At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

10.2.6 Post-study Adverse Event

All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study.

10.2.7 Abnormal Laboratory Values

A clinical laboratory abnormality should be documented as an adverse event if any one of the following conditions is met:

- The laboratory abnormality is not otherwise refuted by a repeat test to confirm the abnormality
- The abnormality suggests a disease and/or organ toxicity
- The abnormality is of a degree that requires active management (e.g., change of dose, discontinuation of the drug, more frequent follow-up assessments, further diagnostic investigation, etc.).

10.2.8 Hospitalization, Prolonged Hospitalization or Surgery

Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for an adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should **not** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

10.6. Assessing and Recording of Adverse Events

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

All adverse events that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

From the time of treatment allocation/randomization through 30 days following cessation of treatment, all adverse events must be reported by the investigator. Such events will be recorded at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in section 10.8. The investigator will make every attempt to follow all subjects with non-serious adverse events for outcome.

Adverse events will not be collected for subjects during the pre-screening period (for determination of archival tissue status) as long as that subject has not undergone any protocol- specified procedure or intervention. If the subject requires a blood draw, fresh tumor biopsy, etc., the subject is first required to provide consent to the main study and AEs will be captured according to guidelines for standard AE reporting.

10.7. Evaluating Adverse Events

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

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

Table 7 Evaluating Adverse Events

V4.0 CTCAE Grading	**Grade 1**	**Mild; asymptomatic or mid symptoms; clinical or diagnostic observations only; intervention not indicated.**
	Grade 2	**Moderate; minimal, local or noninvasive intervention indicated; limiting age-**
	Grade 3	**Severe or medically significant but not immediately life-threatening; hospitalization or prolongation or hospitalization indicated; disabling;**
	Grade 4	**Life threatening consequences; urgent intervention indicated.**
	Grade 5	**Death related to AE**
Seriousness	A serious adverse event is any adverse event occurring at any dose or during any use of Merck product that:	
	†**Results in death**; or	
	†**Is life threatening; or** places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred (Note: This does not include an adverse event that, had it occurred in a	
	†**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to	
	†**Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not a serious adverse event. A pre-existing condition is a clinical condition that	
	†**Is a congenital anomaly/birth defect** (in offspring of subject taking the product regardless of time to	
	Is a new **cancer** (that is not a condition of the study) **(**although not serious per ICH definition, is reportable to the Sponsor within 24 hours and to Merck within 2 working days to meet certain local	
	Is an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event for collection purposes. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported within 24 hours to	
	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the	
Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time	
Action taken	Did the adverse event cause Merck product to be discontinued?	

Relationship to Merck Product	Did Merck product cause the adverse event? The determination of the likelihood that Merck product caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test drug and the adverse event based upon the available information.	
	Exposure	Is there evidence that the subject was actually exposed to Merck product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected
	Time Course	Did the AE follow in a reasonable temporal sequence from administration of Merck product?
	Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other

10.8. Reporting of Serious Adverse Events

10.2.9 IRB Notification by Sponsor-Investigator

Reports of all events (including follow-up information) that meet the definition of an unanticipated problem posing risk to subjects or others must be submitted to the IRB within one week (5 business days) following the occurrence of the unanticipated problem or the principal investigator's acquiring knowledge of the unanticipated problem in accordance with IRB policy. Additionally, the sponsor-investigator will submit a summary of all Unanticipated problems that occurred since the beginning of the study at the time of continuing review. Copies of each report and documentation of IRB notification and receipt will be kept in the Regulatory binder.

10.2.10 FDA Notification by Sponsor-Investigator

The Columbia University Medical Center Sponsor-Investigator, as holder of the IND, will be responsible for all communication with the FDA. Columbia University Medical Center Principal Investigator will report to the FDA, regardless of the site of occurrence, any adverse event that is serious, unexpected and there is evidence to suggest a causal relationship between the drug and the adverse event. These must be reported to the FDA and any affiliate sites as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting. The Sponsor-Investigator will also submit an IND annual report to the FDA in accordance with 21.CFR 312.33.

The Columbia University Medical Center Sponsor Investigator must report to the FDA and any affiliate site investigators as follows:

- Any unexpected fatal or life-threatening event must be reported as soon as possible, but no later than 7 calendar days after the sponsor investigator initial receipt of the information
    - Any findings from epidemiological studies, pooled analysis of multiple studies, or clinical studies, whether or not conducted under an IND, and whether or not conducted by the sponsor-investigator, that suggest a significant risk in humans exposed to the drug must be reported as soon as possible but no later than 15 calendar days after the sponsor-investigator determines that the information qualifies for reporting
    - Any findings from animal or in vitro testing whether or not conducted

under an IND, and whether or not conducted by the sponsor-investigator, that suggest a significant risk in humans exposed to the drug must be reported as soon as possible but no later than 15 calendar days after the sponsor- investigator determines that the information qualifies for reporting

- Any clinically important increase in the rate of a serious suspected adverse reactions over that listed in the protocol or Investigator Brochure
- Expected SAEs and AEs will be included in the IND Annual Reports.

Follow-up information to a safety report should be submitted as soon as the relevant information is available. However, if the results of a sponsor's investigation show that an adverse drug experience not initially determined to be reportable are so reportable, the sponsor investigator

must report such experience as soon as possible, but no later than 15 calendar days after the determination is made.

All other serious unexpected experiences associated with the use of the study treatment will be reported to FDA as soon as possible but in no event later than 15 calendar days after initial receipt of the information.

10.2.11 DSMC Reporting by the Sponsor Investigator

Serious adverse events not constituting unanticipated problems are to be reported to the HICCC DSMC. Reporting should occur within 24 hours of knowledge of the SAE occurring at our institution or affiliate sites.

10.2.12 Reporting to Drug Manufacturer by Sponsor-Investigator

The Sponsor-Investigator will report to investigational agent manufacturer any serious adverse events that meet the reporting criteria to the Institutional Review Board as described in section 10.8.1 and/or to the FDA as described in section 10.8.2 within 72 hours of becoming aware of it, so that these reports can be evaluated and included in the Investigator's Brochure and for IND safety submissions per regulations. Reporting will occur by sending the reporting form along with any additional documentation sent to the regulatory authorities.

At the time of IRB renewal or at the request of the manufacturer, the Sponsor-Investigator will submit a summary of all Serious Adverse Events that have occurred inclusive of all sites to manufacturer.

10.9 Reporting Process

Adverse events may be submitted on FDA Form 3500A, the HICCC DSMC Serious Adverse Event Reporting Form, or in a narrative format.

11.

11.1

11. PHARMACEUTICAL INFORMATION

11.1. Pembrolizumab

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

Clinical Supplies will be provided by the Sponsor as summarized in Table 8.

Clinical supplies will be packaged to support enrollment and replacement subjects as required. When a replacement subject is required, the Sponsor or designee needs to be contacted prior to dosing the replacement supplies.

Table 8 Product Description- Pembrolizumab

Product Name & Potency	Dosage Form	Additional Information
Pembrolizumab 50 mg/vial	Lyophilized powder for injection	Provided centrally by the Sponsor

All supplies indicated in Table 8 will be provided per the Additional Information field depending on local country operational or regulatory requirements.

Any commercially available product not included in Table 8 (i.e. azacitidine) will be provided by the trial site, subsidiary or designee. Every attempt should be made to source these supplies from a single lot/batch number.

The trial site is responsible to record the lot number, manufacturer and expiration date for any locally purchased product as per local guidelines unless otherwise instructed by the Sponsor.

11.2. Packing and Labeling Information

Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements. Subjects will receive open label vials and/or kits for every 3-week dosing.

11.3. Clinical Supplies Disclosure

This trial is open-label; therefore, the subject, the trial site personnel, the Sponsor and/or designee are not blinded. Treatment (name, strength or potency)

is included in the label text; random code/disclosure envelopes or lists are not provided.

11.4. Storage and Handling Requirements

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label. Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site. Clinical supplies may not be used for any purpose other than that stated in the protocol.

11.5. Discard/Destruction/Returns and Reconciliation

The investigator is responsible for keeping accurate records of the clinical supplies received from the Sponsor or designee, the amount dispensed to and returned by the subjects and the amount remaining at the conclusion of the trial. For all trial sites, the local country Sponsor personnel or designee will provide appropriate documentation that must be completed for drug accountability and return, or local discard and destruction if appropriate. Where local discard and destruction is appropriate, the investigator is responsible for ensuring that a local discard/destruction procedure is documented.

11.6. Standard Policies

Trial site personnel will have access to a central electronic randomization system (IVRS/IWRS system) to allocate subjects, to assign treatment to subjects and to manage the distribution of clinical supplies. Each person accessing the IVRS system must be assigned an individual unique PIN. They must use only their assigned PIN to access the system, and they must not share their assigned PIN with anyone.

11.7. Other Agent: Azacitidine

Product description: Azacitidine (Vidaza) at a dose of 50 mg/m^2 by SubQ injection repeated daily for 5 days. Repeat cycle after 4 weeks.

Solution preparation (how the dose is to be prepared): Azacitidine should be aseptically reconstituted with 4 mL of Sterile Water for Injection (USP); upon reconstitution, the resulting suspension will contain azacitidine 25 mg/mL. The reconstituted product may be kept in the vial or drawn into a syringe. Doses greater than 4 mL should be divided equally into 2 syringes.

Storage requirements: The reconstituted product may be held at room temperature for up to 1 hour, but must be administered within 1 hour after reconstitution. If the preparation is for delayed SubQ administration, the product must be refrigerated immediately. When azacitidine is reconstituted using water for injection that has not been refrigerated, the reconstituted product may be held under refrigerated conditions (2°C – 8°C, 36°F – 46°F) for up to 8 hours. When azacitidine is reconstituted using refrigerated (2°C – 8°C, 36°F – 46°F) water for injection, the reconstituted product may be stored under refrigerated

conditions (2°C – 8°C, 36°F – 46°F) for up to 22 hours. After removal from refrigerated conditions, the suspension may be allowed to equilibrate to room temperature for up to 30 minutes prior to administration.

Stability: Azacitidine reconstituted with non-refrigerated water for injection for SubQ administration may be stored for up to 1 hour at 25°C (77°F) or for up to 8 hours between 2°C and 8°C (36°F and 46°F); when reconstituted with refrigerated (2°C – 8°C, 36°F – 46°F) water for injection, it may be stored for 22 hours between 2°C and 8°C (36°F and 46°F).

Route of administration: Azacitidine is administered at a dose of 50 mg/m2 by SubQ injection, rotating sites for each injection (thigh, abdomen, or upper arm), repeated daily for 5 consecutive business days. This cycle should be repeated after 4 weeks. On the days when azacitidine is given with pembrolizumab, the pembrolizumab will be administered first followed by azacitidine.

12. STUDY CALENDAR

12.1. Trial Flow Chart

Baseline evaluations are to be conducted according to the trial flow chart below (Section 12.1). Scans and x-rays must be done $\leq$ 4 weeks prior to the start of therapy. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy.

Trial Period:	Screening Phase	Treatment Cycles [a]										End of Treatment (last dose) or Discontinuation	Post-Treatment		
		Azacitidine (4 weeks per cycle)						Pembrolizumab (3 weeks per cycle)							
Treatment Week:		1	2	3	5	6	8	9	12	15	18		Safety Follow- Up (30 days from last dose)[q]	Follow Up Visits[b] (Q8W)	Survival Follow-Up (Phone)
Scheduling Window (Days):	-28 to -1		± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3				± 7
Administrative Procedures															
Informed Consent [c]	X														
Inclusion/Exclusion Criteria	X														
Demographics and Medical History	X														
Prior and Concomitant Medication Review	X	X		X	X	X		X	X	X	X	X	X		
Clinical Procedures/Assessments															
Review Adverse Events	X			X	X	X		X	X	X	X	X			
12-Lead ECG	X														
Physical Examination	X	X		X	X	X		X	X	X	X	X			
Ht (V1 only), Wt, & Vital Signs (T/P/RR/BP)	X											X			
ECOG Performance Status	X[p]	X		X	X	X		X	X	X	X	X			
Azacitidine Treatment Administration[o]		X			X			X then Q4W							
Pembrolizumab Treatment Administration[o]				X		X		X then Q3W							
Post-study Anticancer Therapy Status														X	Q12W
Survival Status															Q12W
Laboratory Procedures/Assessments: analysis performed by LOCAL laboratory															
Pregnancy Test – Urine or Serum □- HCG[d]	X														
PT/INR and aPTT[e]	X														
CBC with Differential[e,g]	X	X		X	X	X		X	X	X	X	X	X		
Chemistry Panel[e,f]	X	X		X	X	X		X	X	X	X	X	X		
Urinalysis[e]	X														
Amylase and Lipase	X					X		X				X			

Trial Period:	Screening Phase	Treatment Cycles [a]										End of Treatment (last dose) or Discontinuation	Post-Treatment		
		Azacitidine (4 weeks per cycle)						Pembrolizumab (3 weeks per cycle)							
Treatment Week:		1	2	3	5	6	8	9	12	15	18		Safety Follow- Up (30 days from last dose)	Follow Up Visits[b] (Q8W)	Survival Follow-Up (Phone)
Scheduling Window (Days):	-28 to -1		± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3				± 7
T3, FT4 and TSH[c]	X			X		X		X then Q6W				X	X		
Serum CA 19-9[e,h]	X			X		X		X		X then Q6W		X			
HBV, HCV, HIV[e,i]	X														
Efficacy Measurements															
Tumor Imaging	X[j]						X[k] then Q8W					X[l]			
Tumor Biopsies/Archival Tissue Collection/Correlative Studies Blood															
Archival or Newly Obtained Tissue Collection[m]	X						X					X[optional]			
Correlative Studies Blood Collection	X[n]			X	X	X						X			

a. Unless otherwise specified, assessment/procedures are to be performed prior to dose administration on Day 1 of each cycle.
b. Subjects who discontinue study treatment without documented disease progression should continue to be monitored for disease by radiologic imaging every 8 weeks (□7 days) until (1) the start of new anti-cancer treatment, (2) disease progression, (3) death, or (4) the end of the study, whichever occurs first.
c. Informed consent will include consent for correlative studies including biopsies and serum collections.
d. For women of reproductive potential, a negative pregnancy test should be performed within 72 hours prior to first dose of trial treatment. Pregnancy tests (serum and/or urine tests) should be repeated if required by local guidelines.
e. Laboratory Screening Tests should be performed within 7 days prior to first dose of treatment. For all subjects, unresolved abnormal labs resulting in drug-related AEs should be followed until resolution. Post dose lab may be collected up to 72 hours prior to the scheduled timepoint.
f. Chemistry will be collected on Day 1 of each cycle of azacitidine and pembrolizumab.
g. CBC with differentials will be collected on Day 1 of each cycle of azacitidine and pembrolizumab.
h. On treatment CA 19-9 – starting at Cycle 1 of Pembrolizumab, CA 19-9 will be collected Q3W until week 15 then every 2 pembrolizumab cycles (Q6W +/- 2 weeks) through the end of treatment
i. All subjects will be tested for HIV, HBV, and HCV prior to enrollment. Those who are positive for HIV, untreated active Hepatitis B, and dual infection with HBV/HCV will be excluded.
j. Tumor imaging at screening: Imaging will be performed within 28 days prior to the first dose of induction. Imaging should include CT chest, abdomen, and pelvis or MRI if CT is clinically contraindicated.
k.The first-on study tumor imaging will be performed after 8 weeks (±7 days) of treatment, and will continue every 8 weeks (□□7 days) thereafter (or more frequently if clinically indicated). Timing of imaging follows calendar days and should not be adjusted due to dose interruptions. The same imaging technique, acquisition, and processing parameters for a subject should be used throughout the trial if possible.
l. Subjects without confirmed PD who discontinue treatment will have imaging performed at the time study treatment is discontinued (i.e. date of discontinuation □□4 week window). If a scan was obtained within 4 weeks prior to discontinuation of treatment, then imaging at treatment discontinuation is not required. Continue to monitor disease status as indicated in Section 6.6. Subjects who discontinue treatment after confirmed PD will not need further imaging performed during the follow-upperiod.
m. If archival tissue is not available then fresh biopsy is considered any tumor tissue collection within 42 days prior to first dose of study treatment and after previous therapy. All 31 subjects will have a newly-obtained biopsy during week 8 (□□7 days) of the study. An optional biopsy is also requested at the time of discontinuation forPD.

Trial Period:	Screening Phase	Treatment Cycles [a]									End of Treatment (last dose) or Discontinuation	Post-Treatment		
		Azacitidine (4 weeks per cycle)						Pembrolizumab (3 weeks per cycle)						
Treatment Week:		1	2	3	5	6	8	9	12	15	18	Safety Follow- Up (30 days from last dose)[q]	Follow Up Visits[b] (Q8W)	Survival Follow-Up (Phone)
Scheduling Window (Days):	-28 to -1		± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3			± 7

n. Collect at baseline, and then on weeks 3, 5, and 6 prior to study treatment administration. Whole blood for Genetics/RNA and DNA analyses. Serum and plasma for Proteomics.
o. The first dose of azacitidine is Week 1 Day 1, other doses have a +/-3 day window for dose administrations (for azacitidine as well as pembrolizumab). Azacitidine will be dosed on 5 consecutive business days. On the days when azacitidine is given with pembrolizumab, the pembrolizumab will be administered first followed by azacitidine.
p. Screening ECOG should be performed within 3 days prior to first dose of study therapy.
q. Safety follow-up visit should be conducted approximately 30 days after the last dose of trial treatment or before the initiation of a new anti-cancer treatment, whichever comes first.

12.2. Trial Procedures

The Trial Flow Chart - Section 12.1 summarizes the trial procedures to be performed at each visit. Individual trial procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator. Furthermore, additional evaluations/testing may be deemed necessary by the Sponsor and/or Merck for reasons related to subject safety. In some cases, such evaluation/testing may be potentially sensitive in nature (e.g., HIV, Hepatitis C, etc.), and thus local regulations may require that additional informed consent be obtained from the subject. In these cases, such evaluations/testing will be performed in accordance with those regulations.

12.3. Administrative Procedures

12.1.1 Informed Consent

The Investigator must obtain documented consent from each potential subject or each subject's legally acceptable representative prior to participating in a clinical trial.

Consent must be documented by the subject's dated signature or by the subject's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion. A copy of the signed and dated consent form should be given to the subject before participation in the trial.

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

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

12.1.2 Inclusion/Exclusion Criteria

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

12.1.3 Medical History

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

12.1.4 Prior and Concomitant Medications

12.1.4.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-

specified washout requirement, and record prior medication taken by the subject within 28 days before starting the trial. Treatment for the disease for which the subject has enrolled in this study will be recorded separately and not listed as a prior medication.

12.1.4.2 Concomitant Medications

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

12.1.5 Disease Details and Treatments

12.1.5.1 Disease Details

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

12.1.5.2 Prior Treatment Details

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

12.1.5.3 Subsequent Anti-Cancer Therapy Status

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

12.1.6 Clinical Procedures/Assessments

12.1.6.1 Adverse Event (AE) Monitoring

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

Refer to Section 10 for detailed information regarding the assessment and recording of adverse events.

12.1.6.2 Physical Exam

The investigator or qualified designee will perform a complete physical exam during the screening period. Clinically significant abnormal findings should be recorded as medical history. A physical exam should be performed as specified in the Trial Flow Chart (Section 12.1). For subsequent cycles the investigator or qualified designee will perform a directed physical exam as clinically indicated prior to dosing on Day 1 of each treatment cycle. After the first dose of trial treatment new clinically significant abnormal findings should be recorded as AEs.

12.1.6.3 Vital Signs

The investigator or qualified designee will take vital signs at screening, prior to the

administration of each dose of trial treatment and at treatment discontinuation as specified in the

Trial Flow Chart (Section 12.1). Vital signs should include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at screening only.

12.1.6.4 Eastern Cooperative Oncology Group (ECOG) Performance Status

The investigator or qualified designee will assess ECOG status (see Appendix 1) at screening, prior to the administration of each dose of trial treatment and discontinuation of trial treatment as specified in the Trial Flow Chart.

12.1.6.5 Tumor Imaging and Assessment of Disease

CT chest, abdomen, and pelvis with contrast will be performed at baseline screening, prior to the administration of study drugs, and every 8 weeks thereafter.

12.1.6.6 Tumor Tissue Collection and Correlative Studies Blood Sampling

All patients will have tumor biopsy specimens obtained at baseline prior to study drug administration and then during week 8 to assess methylation status and immune response. Peripheral blood will be evaluated for methylation status at baseline and then prior to treatment administration on weeks 3, 5, and 6.

12.1.6.7 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below. Laboratory tests for hematology, chemistry, urinalysis, and others are specified in the Trial Flow Chart (Section 12.1).

Laboratory tests for screening should be performed within 7 days prior to the first dose of treatment. After Cycle 1, pre-dose laboratory procedures can be conducted up to 72 hours prior to dosing. Results must be reviewed by the investigator or qualified designee and found to be acceptable prior to each dose of trial treatment.

13. MEASUREMENT OF EFFECT

13.1. Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be re-evaluated for response every 8 weeks. In addition to a baseline scan, confirmatory scans should also be obtained 8 (not less than 4) weeks following initial documentation of objective response.

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1)[74]. 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 the RECIST criteria.

13.1.1 Definitions of evaluable subjects

Evaluable for toxicity: All patients will be evaluable for toxicity from the time of their first treatment with azacitidine.

Evaluable for DLT assessment: The initial 6 subjects treated with at least 1 cycles (5 doses) of

azacitidine and 1 dose of pembrolizumab will be evaluated for DLT. Subjects who do not complete these doses will be replaced.

Evaluable for PFS- primary outcome: All subjects who receive a single dose of pembrolizumab will be included in the primary outcome analysis of PFS. If subjects are removed from study prior to completing a single dose of pembrolizumab, they will be replaced.

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.)

13.2. Disease Parameters

Measurable disease: Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded for non-nodal lesions and short axis for nodal lesions) as ≥20 mm by chest x-ray, as ≥10 mm with CT scan, or ≥10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters). Tumor lesions that are situated in a previously irradiated area are not considered measurable.

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

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

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts. Cystic lesions thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Target lesions: All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in

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

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

Non-target lesions: All other lesions (or 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, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

13.3. Methods for Evaluation of Measurable Disease

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

The same method of assessment, i.e. CT or MRI, and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.

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 should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

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.

13.4. Response Criteria- RECIST Criteria

13.4.1 Evaluation of Target Lesions

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

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

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

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

13.4.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

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

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase. Although a clear progression of “non-target” lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

13.4.3 Evaluation of Best Overall Response

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

Table 9 Disease Assessment For Patients with Measurable Disease

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

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

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

13.5. Assessment of Disease According to Immune Related RECIST for Solid Tumors

Although this will not be the primary endpoint we will allow subjects to remain on study if they meet the criteria for immune related RECIST as described. The immune related RECIST (irRECIST), is adapted to account for the unique tumor response seen with immunotherapies.[75]

The irRECIST criteria considers index lesions identified at baseline together with new lesions that may occur after the start of treatment and are incorporated into the calculated tumor burden. The appearance of new lesions alone does not constitute PD.

If imaging shows PD, tumor assessment should be repeated 4 weeks later to confirm PD with the option of continuing treatment for clinically stable subjects. Clinically stable will be defined by the following criteria:

- Absence of signs and symptoms indicating disease progression
- No decline in ECOG performance status

- Absence of rapid progression of disease
- Absence of progressive tumor at critical anatomical sites (eg, cord compression) requiring urgent alternative medical intervention
- Absence of disease progression in close proximity to a vital organ.

Subjects must meet the above bulleted criteria for clinically stable disease in order to continue on study treatment beyond initial imaging showing PD. Clinically stable subjects who continue on study treatment will first be reconsented.

In determining whether the tumor burden has increased or decreased, investigators should consider all target lesions as well as non-target lesions. Subjects who are deemed clinically unstable are not required to have repeat imaging for confirmation. If radiologic progression is confirmed, then the subject will be discontinued from study treatment as specified in the Protocol, and the first radiographic evidence of PD should be the date of progression. If radiologic progression is not confirmed, then the subject should resume/ continue study treatment and have their next scan according to the Protocol-specified schedule (ie 4 weeks later and then every 8 weeks). If progression is not confirmed and the subject continues on treatment, the next scan that documents disease progression (and is confirmed by a second scan at least 4 weeks later) will be considered the date
of disease progression.

NOTE: If a subject with confirmed radiographic progression (ie, 2 scans at least 28 days apart demonstrating PD) is clinically stable or clinically improved, and there is no further increase in the tumor dimensions at the confirmatory scan, an exception may be considered to continue treatment upon consultation with the sponsor. In order for a patient to be considered clinically stable, all bulleted criteria listed above in section 13.5 must be fulfilled. Clinically stable subjects should also have at the confirmatory scan no further increase in the target lesions, no unequivocal increase in non-target lesions, and no additional new lesions develop (non-worsening PD) to continue study treatment. Such exceptions will need to be made in consultation with the study Sponsor and the trial's DSMC. However, study treatment continued beyond PD will be discontinued if radiologic progression worsens.

13.5.1 Evaluation of Target Lesions by irRECIST

Tumor burden = Sum of diameter (target) + Sum of diameter (new)

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 tumor burden compared with baseline.

Progressive Disease (PD): At least a 20% increase in the tumor burden compared, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study), with confirmation of progression by a scan at least 4 weeks later (Note: With irRECIST, the appearance of new lesions alone is not 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.

13.5.2 Evaluation of Best Overall Response with irRECIST

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

Measurable Response	**Nonmeasurable Response**		**Overall Response**
Total Measurable Tumor Burden	Non-Index Lesions	New Nonmeasurable Lesions	Using irRECIST
100% Decrease	Absent	Absent	irCR
≥ 30% Decrease	Any	Any	irPR
<30% Decrease to <20% Increase	Any	Any	irSD
≤ 20% Increase	Any	Any	irPD

13.6. Analysis of Endpoints

Efficacy and safety endpoints that will be evaluated are listed below.

13.6.1 Efficacy Endpoints

13.6.1.1 Primary Efficacy Endpoint

- Progression-Free Survival
  - PFS is defined as the time from the first day of trial treatment to the first documented disease progression per RECIST 1.1 or death due to any cause, whichever occurs first.

13.6.1.2 Secondary Efficacy Endpoints

- Objective Response Rate
  - ORR is defined as the proportion of the subjects in the analysis population who have a CR or PR. Responses are based on assessments per RECIST 1.1.
- Duration of Response
  - For subjects who demonstrate CR or PR, based on assessments per RECIST 1.1, DOR is defined as the time from first documented evidence of CR or PR until disease progression or death due to any cause, whichever occurs first.
- Disease Control Rate
  - DCR is defined as the percentage of subjects who have achieved CR, PR, or SD based on assessments per RECIST 1.1.
- Overall Survival (OS)
  - OS is defined as the time from first dose of study medication to death due to any cause.

13.6.2 Safety Endpoints

The primary safety objective of this trial is to characterize the safety and tolerability of pembrolizumab in combination with azacitidine in subjects with advanced pancreatic ductal adenocarcinoma. The primary safety analysis will be based on subjects who experienced toxicities as defined by CTCAE criteria. Safety will be assessed by quantifying the toxicities and grades experienced by subjects who have received pembrolizumab, including serious adverse events (SAEs) and events of clinical interest (ECIs).

Safety will be assessed by reported adverse experiences using CTCAE, Version 4.0. The attribution to study treatment, time-of-onset, duration of the event, its resolution, and any concomitant medications administered will be recorded. AEs will be analyzed including but not limited to all AEs, SAEs, fatal AEs, and laboratory changes. Furthermore, specific immune-related adverse events (irAEs) will be collected and designated as immune-related events of clinical interest (ECIs) as described in Section 10.4.

13.6.3 Correlative Endpoints

13.6.3.1 Global DNA Methylation

DNA methylation, using LINE-1 assay, will be determined and expressed as continuous variables with mean, median, and standard deviation calculations reported. Average changes in global DNA methylation will be assessed at baseline and every two weeks for the first eight weeks of the study. Disease control rates (DCR) and time to event endpoints (PFS and OS) will

be estimated for patients who have methylation below the median compared to above the median at baseline. We will also estimate these outcomes for those who achieve low methylation (<10% methylation) compared to normal methylation (≥10% methylation) after eight weeks of therapy. We will also estimate these outcomes for those who achieve a change in methylation greater than the median compared to lower than the median at eight weeks compared to baseline.

13.6.3.2 Epigenetic effect in tumor tissue

The premise of our proposal is that hypomethylation of tumor cells and/or stromal cells results in a significant polarization of the immune response seen in pancreatic cancer and this leads to an increase in response to tumor checkpoint inhibition. Our preliminary data provides strong support for this, however this study provides a unique opportunity to understand the dynamic changes that occur in the tumor. Therefore we will first assess the impact of the systemically administered demethylating agent on tumor tissue. This assessment is performed in all 31 patients 8 weeks after completion of TCI therapy. Core biopsies are obtained and tumor tissue is microdissected for methylation profiling using the Illumina 800K platform. Comparison is made to the pre-treatment tumor biopsy. The Herbert Irving Comprehensive Cancer Center Epigenetics Core Laboratory (led by co-investigator Benjamin Tycko, MD, PhD) routinely performs this procedure and the subsequent statistical analysis and mapping of the resulting data to ENCODE tracks. Validation of up to 48 amplicons in up to 48 samples is done using the Fluidigm Access Array – Illumina MiSEQ platform. Here, bisulfite treatment and sequencing is performed to validate “hits” from the methylation array.

A subsequent validation step at the transcriptional and translational level will be performed

based on the classes of genes identified but include one of three strategies (1) RNASeq; (2) Q-PCR; (3) immunohistochemistry or immunofluorescence on concurrent biopsy specimens. In cases where sufficient quantity of tumor material is obtained to perform RNASeq analysis this will be pursued. The parallel use of methylation and expression profiling allows for the selection of functionally most relevant genes. Although there is support for the feasibility of sufficient amount of high quality RNA obtained from endoscopic biopsies to perform RNASeq as we are uncertain whether in each case this will be feasible the alternative strategies may also bepursued.

13.6.3.3 **Immune phenotyping**

It is our hypothesis that azacitidine will have significant impact on immune polarization in the tumor and potentially the number of PD1 or PDL1 positive cells. We have recently shown and validated the ability to score expression of epithelial markers and inflammatory cell markers in pancreatic cancer endoscopic core biopsies. We therefore will evaluate the expression of the ratio of CD8/CD3 T cells, CD86/CD68 macrophages and PD1 and PD1L expression using immunohistochemistry.

The ratio of CD8/CD3 TILs and CD86/CD68 macrophages will be calculated and expressed as a continuous variable with mean, median, and standard deviation calculations reported. We will compare pre- and post-treatment CD8/CD3 and CD86/CD68 ratios using a paired t-test or a nonparametric test based on the data distribution.

PD-L1 expression at baseline will be quantified as a dichotomous variable (>1% expression

considered positive, <1% considered negative). PD-L1 expression is reported to be higher in 81% of pancreatic tumors in historical controls than in paired non-malignant samples[26]. Correlation between baseline PD-L1 expression (positive vs. negative) and response to therapy (patients with clinical benefit, as defined by radiographic response and disease control, and those without clinical benefit) will be analyzed using frequency tables and Fisher's exact test.

13.7. Unblinding Procedures

N/A- this is not a blinded study.

13.8. Stopping Rules

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

- Unacceptable aggregate toxicity as determined by the trial's Sponsor in consultation with the trial's DSMC
- Quality or quantity of data recording is inaccurate or incomplete
- Poor adherence to protocol and regulatory requirements
- Incidence or severity of adverse drug reaction in this or other studies indicates a potential health hazard to subjects
- Plans to modify or discontinue the development of the study drug

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

14. DATA REPORTING / REGULATORY REQUIREMENTS

14.1. Data Collection

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 10.0 (Adverse Events: List and Reporting Requirements). The Data Safety Monitoring Plan is described in Section 14.3.

The Herbert Irving Comprehensive Cancer Center has an electronic clinical trials and data management system (CTMS) that will be used for data collection. CRFs for the study will be built into the CTMS for data entry. The system has full auditing capabilities which is web-based and housed on a server in a fully HIPAA compliant server room with restricted access and video camera monitoring. All users must login with their own application username and password. Users off campus must first access the Virtual Private Network with their assigned campus username and password and then use their application credentials. Users are only able to see study information if they are indicated as study personnel in our electronic IRB system. Users are limited to access based on the role assigned in their corresponding protocol. Subject data is entered directly into the system, which (in the case of Columbia subjects) confirms the correct identity of patients via an interface with the electronic medical patient index. Staff with the appropriate IRB defined roles can run reports within the system for reporting purposes.

14.2. Data Reporting

Case Report Forms will be completed for each subject enrolled into the clinical study through the CTMS. It is the investigator's responsibility for ensuring that all clinical and laboratory data

entered on the corresponding CRFs are complete, accurate and authentic.

14.3. Data and Safety Monitoring Committee

The NCI-approved Data Safety and Monitoring Committee (DSMC) of the Herbert Irving Comprehensive Cancer Center (HICCC) will monitor every subject who receives treatment on this protocol for toxicity. This protocol will adhere to the policies of the currently approved HICCC Data and Safety Monitoring Plan (DSMP), which is in accordance with NCI and CUMC-IRB policy and guidelines. The committee is chair is appointed by the HICCC Director. The committee consists of HICCC faculty and staff with expertise in oncology, research pharmacy, research nursing, and data management. The DSMC convenes twice a month to review patient safety and the conduct of the trial. The PI will submit data and safety monitoring reports to the DSMC at a frequency to be determined by the DSMC based on risk to the subjects.

At the time of renewal, the study team will submit the most recent DSMC approval letter for safety review to the CUMC IRB. Any modifications that are required by the DSMC to ensure patient safety will be submitted to the IRB. All protocol deviations, violations, and eligibility

waivers will be submitted to and approved by the DSMC prior to being reported to the IRB. All study data reviewed and discussed during these meetings will be kept confidential.

For multicenter research, the principal investigator will assure that there is a mechanism in place to distribute the report to all participating investigators for submission to their local IRB. The report will document that a review of data and outcomes across all centers took place on a given date. It will summarize the DSMC's review of the cumulative toxicities reported from all participating sites without specific disclosure by treatment arm. It will also inform site investigators of the study the DSMC's conclusion with respect to progress or need for modification of the protocol.

14.4. Quality Control and Quality Assurance

Independent monitoring of the clinical study for protocol and GCP compliance will be conducted periodically by the CPDM Compliance Core on behalf of the HICCC DSMC. Additionally, the Compliance Oversight Committee of the IRB at Columbia University Medical Center may audit the study at any time per institutional policies and procedures. The investigator-sponsor and Columbia University Medical Center will permit direct access of the study monitors and appropriate regulatory authorities to the study data and to the corresponding source data and documents to verify the accuracy of this data.

A risk-based approach will be used by the Compliance Core to determine the frequency, number of subject charts, and data elements to be monitored. The Compliance Coordinator will review the study status and summarize enrollment, toxicities, SAEs/UPs, dose escalation, statistical endpoints (e.g., stopping rules), etc. for the full DSMC membership at the regularly scheduled meetings.

Internal On-site Monitoring:

- Initial, recurrent, and close-out on-site monitoring visits will also be conducted at remote clinical sites, as appropriate/feasible. Other sites will have monitoring performed remotely (see below for further details).
- The study Monitoring Visit Log will be completed and signed by the monitor and the PI/CRNP/CRN and/or CRC and will be filed in the regulatory binder.
- The Compliance Coordinator will communicate with the site coordinator/Site Principle Investigator to schedule the monitoring visit and arrange for access to study materials and documentation.
- The assigned Compliance Coordinator will monitor IIT trials within 1 month after the first subject is enrolled and throughout the life of the study to ensure that the study is being conducted in accordance with the protocol, GCP, applicable federal and local regulations, and per all applicable SOPs. The Compliance Coordinator is responsible to notify the PI and CRNP/CRN/CRC of upcoming monitor visits and convey what information and documentation will be required for the visit(s). The Compliance Coordinator is responsible for verifying that informed consent is properly obtained, eligibility is met (via the central registration process), and all study procedures are conducted according to the study protocol. The Compliance Coordinator will also verify

that the data reported in the CRF's accurately reflect source documents, that all toxicities have been reported to date, and that all SAE's/UPs/deviations/violations have been reported according to local IRB and HICCC DSMC requirements. The Compliance Coordinator will issue queries and ensure resolution in a timely and efficient manner. The Compliance Coordinator will also monitor for applicable regulatory compliance and research pharmacy compliance (if applicable) and communicate any deficiencies as appropriate.

14.5. Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (e.g., that the subject is alive) at the end of their scheduled study period.

The subject binders will be maintained with in the CPDM offices, a secured floor within the

Herbert Irving Pavilion and only the investigator and study staff will have access to the file.

14.6. Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

14.7. Case Report Forms

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A".

14.8. Records Retention

Records relating to a specific research activity, including research records collected by investigators, must be maintained for at least three years after completion of the research (45 CFR 46.115(b); 21 CFR 56.115(b); 21 CFR 312.62). This minimum retention period applies whether or not any subjects were enrolled in the study.

If the research is FDA regulated, records should be retained for at least two years after approval of the investigational agent by FDA; if it is not approved, records should be retained at least two years after the study is terminated and FDA is notified (note the additional requirement below for clinical research studies).

Clinical records, including consent forms that document clinical intervention or clinical diagnostic procedure research-related procedures, must be retained in medical records by the institution for at least seven years, per CUMC and NYP policy which is based on state law.

15. STATISTICAL CONSIDERATIONS

15.1. Statistical Analysis Plan Summary

This statistical analysis plan was developed in collaboration with the study statistician, Shing Lee, Ph.D.

15.2. Populations for Statistical Analysis and Reporting

15.2.1 DLT Evaluable Population

The DLT Evaluable Population consists of subjects in the initial 6 patient DLT cohort who complete at least 5 doses of azacitidine and 1 dose of pembrolizumab and completed the DLT observation period (6 weeks), and those who did not complete the DLT observation period and discontinued from study treatment due to a DLT event. The DLT Evaluable Population will be used for DLT assessments.

15.2.2 Safety Population

The Safety Population consists of all subjects treated with at least one dose of any study drug. The Safety Population for azacitidine consists of all subjects treated with at least one dose of azacitidine, and will be used for the analysis of the safety data. The Safety Population for pembrolizumab consists of all subjects treated with at least one dose of pembrolizumab, and will be used for the analysis of the safety data.

15.2.3 Efficacy Population

Evaluable for PFS- primary outcome: All subjects who receive a single dose of protocol therapy will be included in the primary outcome analysis of PFS. If subjects are removed from study prior to completing a single dose of pembrolizumab, they will be replaced but will be included in the primary analysis.

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.)

15.2.4 Reporting of Outcomes

All conclusions should be based on all eligible patients. Sub analyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (e.g., early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.). However, these sub analyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis should be clearly reported. The 95% confidence intervals should also be provided.

15.3. Study Design/Endpoints

15.2.5 Primary Endpoint

The primary hypothesis of this study is that combination hypomethylation induction followed by PD-1 blockade maintenance will result in increased efficacy compared to standard of care chemotherapy. This will be evaluated by comparing time to disease recurrence or death in this study with historical controls. This is based on recent studies evaluating therapy options after failure of first-line therapy in metastatic pancreatic cancer. The recently completed cooperative group study (SWOG S1115[6]) was designed to evaluate an experimental therapy compared to standard chemotherapy with a null hypothesis of median PFS of 2 months. The study was a negative study and as reported in December 2016 both arms resulted in PFS of around 2 months in this setting.

The **primary endpoint** is progression-free survival defined as the time from first treatment with the study drug to the earliest of either disease progression or death from any cause. Patients who are alive and progression free at the time of analysis will be censored at the time of their last follow-up. With 31 eligible subjects enrolling over 18 months with an additional 6 months of follow-up, we will have 80% power to detect a median PFS of 2 months in historical controls versus 4 months with one-sided alpha of 0.05.

The Kaplan-Meir method will be used to evaluate all time to event endpoints. Median progression-free survival will be reported with 95% confidence intervals.

15.2.6 Secondary Endpoints

The secondary hypothesis of this study is that combination therapy will lead to improvements in overall response rate (ORR), duration of response (DOR), disease control rate (DCR), and overall survival (OS). These will all be reported with percentages and 95% confidence intervals. The Kaplan-Meir method will be used to evaluate all time to event endpoints.

15.2.6.1 Definition of secondary endpoints:

- **Objective Response Rate**
    - ORR is defined as the proportion of the subjects in the analysis population who have a CR or PR. Responses are based on assessments per RECIST 1.1 as described in Section 13.4.

- **Duration of Response**
  - For subjects who demonstrate CR or PR, based on assessments per RECIST 1.1, DOR is defined as the time from first documented evidence of CR or PR until disease progression or death due to any cause, whichever occurs first.
- **Disease Control Rate**
  - DCR is defined as the percentage of subjects who have achieved CR, PR, or SD based on assessments per RECIST 1.1.
- **Overall Survival (OS)**
  - OS is defined as the time from first dose of study medication to death due to any cause.

15.2.7 Exploratory and Ancillary Studies

See Section 13.6.3 for description of correlative studies. All subjects will be required to agree to an on treatment biopsy after 8 weeks of therapy. Given the patient population and the likelihood that some subjects will have disease or clinical progression precluding biopsies we estimate that we will obtain on-treatment biopsy samples from a minimum of 20 subjects.

15.2.7.1 Global DNA Methylation will be assessed in all subjects at baseline and every 2 weeks for the first 8 weeks of study. We will estimate the disease control rates (DCR) and time to event endpoints (median PFS and median OS) for subjects who have methylation below the median compared to above the median at baseline. We will also estimates these outcomes for those who achieve low methylation (<10% methylation) compared to normal methylation (≥10% methylation) after 8 weeks of therapy. We will also estimates these outcomes for those who achieve a change in methylation greater than the median compared to higher than the median at 8 weeks (compared to baseline).

15.2.7.2 Fisher's exact test will be performed to compare the disease control rate for the two groups. Kaplan-Meier estimates of the survival distribution for the two groups will be calculated, and the two groups will be compared using a log-rank test. Change in methylation in tumor tissue will be evaluated in 20 patients who undergo baseline and week eight biopsies and will be compared using the paired t-test or the Wilcoxon signed-rank test depending on the data distribution. With 20 patients, we will have 80% power to detect a change of 0.66 standard deviations given an alpha of 0.05.

15.2.7.3 Change in methylation in tumor tissue will be evaluated in subjects who undergo baseline and week 8 biopsies. We will describe changes in specific gene methylation patterns as described in Section 13.6.3.

15.2.7.4 Immune phenotyping will be measured on the subjects who undergo an on-treatment tumor biopsy. We will provide descriptive tables of IHC expression of CD8/CD3 T cell ratio, CD86/CD68 macrophage ratio, PD1 expression. Samples will be compared between pre and post combination specimens in treated subjects using the paired t-test.

15.4. Size/Accrual Rate

A total of 31 subjects will be enrolled over 18 months with plan to screen 4-5 subjects in our

multi-disciplinary pancreas clinic each month with enrollment of 2-3 patients per month. If the original 6 patient DLT cohort requires a dose reduction then up to a maximum of 37 subjects will be enrolled with 31 additional enrolled at the final dose level.

15.5. Stratification Factors

No stratification is planned.

15.6. Statistical Methods for Safety Analysis

Safety and tolerability will be assessed by clinical review of all relevant parameters including adverse experiences (AEs), laboratory tests, and vital signs. Count and percentage AE will be provided. Confidence interval rate of AE of clinical interest will be estimated using Exact method based on binomial distribution.

15.7. Analysis Populations

All subjects who received at least one dose of study treatment will be included in the primary and secondary efficacy and safety analysis as detailed in Section 15.2.

16. PROTECTION OF HUMAN SUBJECTS

This study is to be conducted in accordance with applicable government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be obtained before commencement of this study.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB for the study. The formal consent of a subject, using the IRB-approved consent form, must be obtained before that subject is submitted to any study procedure. This consent form must be signed by the subject or legally acceptable surrogate, as outlined in the IRB approved protocol, and the investigator-designated research professional obtaining the consent.

17. STUDY FINANCES

17.1. Conflict of Interest

N/A

17.2 Subject Stipends or Payments

N/A

18. PUBLICATION PLAN

Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by the sponsor for the purposes of performing the study, will be published or passed on to any third party without the consent of the study sponsor. Anyinvestigator involved with this study is obligated to provide the sponsor with complete test results and all data derived from the study.

19. REFERENCES

1. Cohen AL, Ray A, Van Brocklin M, et al. A phase I trial of azacitidine and nanoparticle albumin bound paclitaxel in patients with advanced or metastatic solid tumors. *Oncotarget.* Dec 26 2016.
2. Miller KD, Siegel RL, Lin CC, et al. Cancer treatment and survivorship statistics, 2016. *CA Cancer J Clin.* Jun 2 2016.
3. Von Hoff DD, Ervin T, Arena FP, et al. Increased survival in pancreatic cancer with nab- paclitaxel plus gemcitabine. *The New England journal of medicine.* Oct 31 2013;369(18):1691-1703.
4. Oettle H, Post S, Neuhaus P, et al. Adjuvant chemotherapy with gemcitabine vs observation in patients undergoing curative-intent resection of pancreatic cancer: a randomized controlled trial. *JAMA : the journal of the American Medical Association.* Jan 17 2007;297(3):267-277.
5. Sohal DP, Walsh RM, Ramanathan RK, Khorana AA. Pancreatic adenocarcinoma: treating a systemic disease with systemic therapy. *J Natl Cancer Inst.* Mar 2014;106(3):dju011.
6. Chung V, McDonough S, Philip PA, et al. Effect of Selumetinib and MK-2206 vs Oxaliplatin and Fluorouracil in Patients With Metastatic Pancreatic Cancer After Prior Therapy: SWOG S1115 Study Randomized Clinical Trial. *JAMA oncology.* Dec 15 2016.
7. Nakano O, Sato M, Naito Y, et al. Proliferative activity of intratumoral CD8(+) T-lymphocytes as a prognostic factor in human renal cell carcinoma: clinicopathologic demonstration of antitumor immunity. *Cancer Res.* Jul 1 2001;61(13):5132-5136.
8. Burt BM, Rodig SJ, Tilleman TR, Elbardissi AW, Bueno R, Sugarbaker DJ. Circulating and tumor-infiltrating myeloid cells predict survival in human pleural mesothelioma. *Cancer.* Nov 15 2011;117(22):5234-5244.
9. Mu CY, Huang JA, Chen Y, Chen C, Zhang XG. High expression of PD-L1 in lung cancer may contribute to poor prognosis and tumor cells immune escape through suppressing tumor infiltrating dendritic cells maturation. *Medical oncology.* Sep 2011;28(3):682-688.
10. Thompson RH, Gillett MD, Cheville JC, et al. Costimulatory molecule B7-H1 in primary and metastatic clear cell renal cell carcinoma. *Cancer.* Nov 15 2005;104(10):2084-2091.
11. Thompson RH, Kuntz SM, Leibovich BC, et al. Tumor B7-H1 is associated with poor

prognosis in renal cell carcinoma patients with long-term follow-up. *Cancer Res.* Apr 1 2006;66(7):3381-3385.
12. Krambeck AE, Dong H, Thompson RH, et al. Survivin and b7-h1 are collaborative predictors of survival and represent potential therapeutic targets for patients with renal cell carcinoma. *Clin Cancer Res.* Mar 15 2007;13(6):1749-1756.
13. Nomi T, Sho M, Akahori T, et al. Clinical significance and therapeutic potential of the programmed death-1 ligand/programmed death-1 pathway in human pancreatic cancer. *Clinical cancer research : an official journal of the American Association for Cancer Research.* Apr 1 2007;13(7):2151-2157.
14. Loos M, Giese NA, Kleeff J, et al. Clinical significance and regulation of the costimulatory molecule B7-H1 in pancreatic cancer. *Cancer letters.* Sep 8 2008;268(1):98-109.
15. Hamanishi J, Mandai M, Iwasaki M, et al. Programmed cell death 1 ligand 1 and tumor-infiltrating CD8+ T lymphocytes are prognostic factors of human ovarian cancer. *Proceedings of the National Academy of Sciences of the United States of America.* Feb 27 2007;104(9):3360-3365.
16. Andorsky DJ, Yamada RE, Said J, Pinkus GS, Betting DJ, Timmerman JM. Programmed death ligand 1 is expressed by non-hodgkin lymphomas and inhibits the activity of tumor-associated T cells. *Clin Cancer Res.* Jul 1 2011;17(13):4232-4244.
17. Brusa D, Serra S, Coscia M, et al. The PD-1/PD-L1 axis contributes to T-cell dysfunction in chronic lymphocytic leukemia. *Haematologica.* Jun 2013;98(6):953-963.
18. Keir ME, Butte MJ, Freeman GJ, Sharpe AH. PD-1 and its ligands in tolerance and immunity. *Annual review of immunology.* 2008;26:677-704.
19. Park JJ, Omiya R, Matsumura Y, et al. B7-H1/CD80 interaction is required for the induction and maintenance of peripheral T-cell tolerance. *Blood.* Aug 26 2010;116(8):1291-1298.
20. Zou W, Chen L. Inhibitory B7-family molecules in the tumour microenvironment. *Nat Rev Immunol.* Jun 2008;8(6):467-477.
21. Weber JS, Kahler KC, Hauschild A. Management of immune-related adverse events and kinetics of response with ipilimumab. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* Jul 20 2012;30(21):2691-2697.
22. McDermott DF. Immunotherapy of metastatic renal cell carcinoma. *Cancer.* May 15 2009;115(10 Suppl):2298-2305.
23. Kresowik TP, Griffith TS. Bacillus Calmette-Guerin immunotherapy for urothelial carcinoma of the bladder. *Immunotherapy.* Mar 2009;1(2):281-288.
24. Bograd AJ, Suzuki K, Vertes E, et al. Immune responses and immunotherapeutic interventions in malignant pleural mesothelioma. *Cancer immunology, immunotherapy : CII.* Nov 2011;60(11):1509-1527.
25. Topalian SL, Hodi FS, Brahmer JR, et al. Safety, activity, and immune correlates of anti- PD-1 antibody in cancer. *The New England journal of medicine.* Jun 28 2012;366(26):2443-2454.
26. Robert C, Long GV, Brady B, et al. Nivolumab in previously untreated melanoma without BRAF mutation. *The New England journal of medicine.* Jan 22 2015;372(4):320- 330.
27. Weber JS, D'Angelo SP, Minor D, et al. Nivolumab versus chemotherapy in patients

with advanced melanoma who progressed after anti-CTLA-4 treatment (CheckMate 037): a randomised, controlled, open-label, phase 3 trial. *Lancet Oncol.* Apr 2015;16(4):375-384.
28. Brahmer J, Reckamp KL, Baas P, et al. Nivolumab versus Docetaxel in Advanced Squamous-Cell Non-Small-Cell Lung Cancer. *The New England journal of medicine.* May 31 2015.
29. Garon EB, Rizvi NA, Hui R, et al. Pembrolizumab for the treatment of non-small-cell lung cancer. *The New England journal of medicine.* May 21 2015;372(21):2018-2028.
30. Robert C, Schachter J, Long GV, et al. Pembrolizumab versus Ipilimumab in Advanced Melanoma. *The New England journal of medicine.* Jun 25 2015;372(26):2521-2532.
31. Motzer RJ, Rini BI, McDermott DF, et al. Nivolumab for Metastatic Renal Cell Carcinoma: Results of a Randomized Phase II Trial. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* May 1 2015;33(13):1430-1437.
32. Royal RE, Levy C, Turner K, et al. Phase 2 trial of single agent Ipilimumab (anti-CTLA-4) for locally advanced or metastatic pancreatic adenocarcinoma. *J Immunother.* Oct 2010;33(8):828-833.
33. Cheng X, Blumenthal RM. Mammalian DNA methyltransferases: a structural perspective. *Structure.* Mar 2008;16(3):341-350.
34. Cross SH, Bird AP. CpG islands and genes. *Curr Opin Genet Dev.* Jun 1995;5(3):309-314.
35. Jones PA, Baylin SB. The epigenomics of cancer. *Cell.* Feb 23 2007;128(4):683-692.
36. Baylin SB, Jones PA. A decade of exploring the cancer epigenome - biological and translational implications. *Nat Rev Cancer.* Oct 2011;11(10):726-734.
37. Singh M, Maitra A. Precursor lesions of pancreatic cancer: molecular pathology and clinical implications. *Pancreatology.* 2007;7(1):9-19.
38. Rosty C, Geradts J, Sato N, et al. p16 Inactivation in pancreatic intraepithelial neoplasias (PanINs) arising in patients with chronic pancreatitis. *Am J Surg Pathol.* Dec 2003;27(12):1495-1501.
39. Sato N, Fukushima N, Maitra A, et al. Discovery of novel targets for aberrant methylation in pancreatic carcinoma using high-throughput microarrays. *Cancer Res.* Jul 1 2003;63(13):3735-3742.
40. Li H, Chiappinelli KB, Guzzetta AA, et al. Immune regulation by low doses of the DNA methyltransferase inhibitor 5-azacitidine in common human epithelial cancers. *Oncotarget.* Feb 15 2014;5(3):587-598.
41. Kim K, Skora AD, Li Z, et al. Eradication of metastatic mouse cancers resistant to immune checkpoint blockade by suppression of myeloid-derived cells. *Proceedings of the National Academy of Sciences of the United States of America.* Aug 12 2014;111(32):11774-11779.
42. Scanlan MJ, Gure AO, Jungbluth AA, Old LJ, Chen Y-T. Cancer/testis antigens: an expanding family of targets for cancer immunotherapy. *Immunological Reviews.* 2002;188(1):22-32.
43. James SR, Link PA, Karpf AR. Epigenetic regulation of X-linked cancer/germline antigen genes by DNMT1 and DNMT3b. *Oncogene.* Nov 2 2006;25(52):6975-6985.
44. Vlkova V, Stepanek I, Hruskova V, et al. Epigenetic regulations in the IFNgamma signalling pathway: IFNgamma-mediated MHC class I upregulation on tumour cells is associated with DNA demethylation of antigen-presenting machinery genes. *Oncotarget.*

Aug 30 2014;5(16):6923-6935.
45. Toor AA, Payne KK, Chung HM, et al. Epigenetic induction of adaptive immune response in multiple myeloma: sequential azacitidine and lenalidomide generate cancer testis antigen-specific cellular immunity. *British journal of haematology.* Sep 2012;158(6):700-711.
46. Weber J, Salgaller M, Samid D, et al. Expression of the MAGE-1 tumor antigen is up-regulated by the demethylating agent 5-aza-2'-deoxycytidine. *Cancer Res.* Apr 1 1994;54(7):1766-1771.
47. Dubovsky JA, McNeel DG. Inducible expression of a prostate cancer-testis antigen, SSX- 2, following treatment with a DNA methylation inhibitor. *The Prostate.* Dec 1 2007;67(16):1781-1790.
48. Smith HA, Cronk RJ, Lang JM, McNeel DG. Expression and immunotherapeutic targeting of the SSX family of cancer-testis antigens in prostate cancer. *Cancer Res.* Nov 1 2011;71(21):6785-6795.
49. Rao M, Chinnasamy N, Hong JA, et al. Inhibition of histone lysine methylation enhances cancer-testis antigen expression in lung cancer cells: implications for adoptive immunotherapy of cancer. *Cancer Res.* Jun 15 2011;71(12):4192-4204.
50. Wrangle J, Wang W, Koch A, et al. Alterations of immune response of Non-Small Cell Lung Cancer with Azacytidine. *Oncotarget.* Nov 2013;4(11):2067-2079.
51. Gettinger SN, Kowanetz M, Koeppen H, et al. Molecular, immune and histopathological characterization of NSCLC based on PDL1 expression on tumor and immune cells and association with response to the anti-PDL1 antibody MPDL3280A. *ASCO Meeting Abstracts.* May 18, 2015 2015;33(15_suppl):3015.
52. Yang H, Bueso-Ramos C, DiNardo C, et al. Expression of PD-L1, PD-L2, PD-1 and CTLA4 in myelodysplastic syndromes is enhanced by treatment with hypomethylating agents. *Leukemia.* Jun 2014;28(6):1280-1288.
53. Shakya R, Gonda T, Quante M, et al. Hypomethylating therapy in an aggressive stroma-rich model of pancreatic carcinoma. *Cancer Res.* Jan 15 2013;73(2):885-896.
54. Lubbert M, Suciu S, Baila L, et al. Low-dose decitabine versus best supportive care in elderly patients with intermediate- or high-risk myelodysplastic syndrome (MDS) ineligible for intensive chemotherapy: final results of the randomized phase III study of the European Organisation for Research and Treatment of Cancer Leukemia Group and the German MDS Study Group. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* May 20 2011;29(15):1987-1996.
55. Fenaux P, Mufti GJ, Hellstrom-Lindberg E, et al. Efficacy of azacitidine compared with that of conventional care regimens in the treatment of higher-risk myelodysplastic syndromes: a randomised, open-label, phase III study. *Lancet Oncol.* Mar 2009;10(3):223-232.
56. Juergens RA, Wrangle J, Vendetti FP, et al. Combination epigenetic therapy has efficacy in patients with refractory advanced non-small cell lung cancer. *Cancer discovery.* Dec 2011;1(7):598-607.
57. Disis ML. Immune regulation of cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* Oct 10 2010;28(29):4531-4538.
58. Dong H, Strome SE, Salomao DR, et al. Tumor-associated B7-H1 promotes T-cell apoptosis: a potential mechanism of immune evasion. *Nature medicine.* Aug 2002;8(8):793-800.

59. Sharpe AH, Freeman GJ. The B7-CD28 superfamily. *Nature reviews. Immunology.* Feb 2002;2(2):116-126.
60. Brown JA, Dorfman DM, Ma FR, et al. Blockade of programmed death-1 ligands on dendritic cells enhances T cell activation and cytokine production. *Journal of immunology.* Feb 1 2003;170(3):1257-1266.
61. Thompson RH, Dong H, Lohse CM, et al. PD-1 is expressed by tumor-infiltrating immune cells and is associated with poor outcome for patients with renal cell carcinoma. *Clinical cancer research : an official journal of the American Association for Cancer Research.* Mar 15 2007;13(6):1757-1761.
62. Talmadge JE, Donkor M, Scholar E. Inflammatory cell infiltration of tumors: Jekyll or Hyde. *Cancer metastasis reviews.* Dec 2007;26(3-4):373-400.
63. Hodi FS, Dranoff G. The biologic importance of tumor-infiltrating lymphocytes. *Journal of cutaneous pathology.* Apr 2010;37 Suppl 1:48-53.
64. Lee HE, Chae SW, Lee YJ, et al. Prognostic implications of type and density of tumour-infiltrating lymphocytes in gastric cancer. *British journal of cancer.* Nov 18 2008;99(10):1704-1711.
65. Leffers N, Gooden MJ, de Jong RA, et al. Prognostic significance of tumor-infiltrating T- lymphocytes in primary and metastatic lesions of advanced stage ovarian cancer. *Cancer immunology, immunotherapy : CII.* Mar 2009;58(3):449-459.
66. Hiraoka N. Tumor-infiltrating lymphocytes and hepatocellular carcinoma: molecular biology. *International journal of clinical oncology.* Dec 2010;15(6):544-551.
67. Polcher M, Braun M, Friedrichs N, et al. Foxp3(+) cell infiltration and granzyme B(+)/Foxp3(+) cell ratio are associated with outcome in neoadjuvant chemotherapy-treated ovarian carcinoma. *Cancer immunology, immunotherapy : CII.* Jun 2010;59(6):909-919.
68. Okazaki T, Maeda A, Nishimura H, Kurosaki T, Honjo T. PD-1 immunoreceptor inhibits B cell receptor-mediated signaling by recruiting src homology 2-domain-containingtyrosine phosphatase 2 to phosphotyrosine. *Proceedings of the National Academy of Sciences of the United States of America.* Nov 20 2001;98(24):13866-13871.
69. Karpf AR, Peterson PW, Rawlins JT, et al. Inhibition of DNA methyltransferase stimulates the expression of signal transducer and activator of transcription 1, 2, and 3 genes in colon tumor cells. *Proceedings of the National Academy of Sciences of the United States of America.* Nov 23 1999;96(24):14007-14012.
70. Karpf AR, Lasek AW, Ririe TO, Hanks AN, Grossman D, Jones DA. Limited gene activation in tumor and normal epithelial cells treated with the DNA methyltransferase inhibitor 5-aza-2'-deoxycytidine. *Molecular pharmacology.* Jan 2004;65(1):18-27.
71. Matei D, Fang F, Shen C, et al. Epigenetic resensitization to platinum in ovarian cancer. *Cancer research.* May 1 2012;72(9):2197-2205.
72. Chiappinelli KB, Strissel PL, Desrichard A, et al. Inhibiting DNA Methylation Causes an Interferon Response in Cancer via dsRNA Including Endogenous Retroviruses. *Cell.* Aug 27 2015;162(5):974-986.
73. Nishino M, Giobbie-Hurder A, Gargano M, Suda M, Ramaiya NH, Hodi FS. Developing a common language for tumor response to immunotherapy: immune-related response criteria using unidimensional measurements. *Clinical cancer research : an official journal of the American Association for Cancer Research.* Jul 15 2013;19(14):3936-

3943.
74. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *European journal of cancer.* Jan 2009;45(2):228-247.
75. Bohnsack O, Hoos A, Ludajc K. Adaptation of the Immune Related Response Criteria: IRRECIST. *Annals of Oncology.* 2014;25 (Supplement 4):iv369.

20. APPENDICES

20.1. Appendix 1- ECOG Performance Status

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

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20.2. Appendix 2- Common Terminology Criteria for Adverse Events V4.0 (CTCAE)

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for adverse event reporting.

http://www.oncology.tv/SymptomManagement/NationalCancerInstituteUpdatesCTCAEtov403.a spx

20.3. Appendix 3- Response Evaluation Criteria in Solid Tumors (RECIST) 1.1

Criteria for Evaluating Response in Solid Tumors RECIST version 1.1[74] will be used in this study for assessment of tumor response. While either CT or MRI may be utilized, as per RECIST 1.1, CT is the preferred imaging technique in this study.

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