SPONSOR: MIAMI CANCER INSTITUTE AT BAPTIST HEALTH, INC.

TITLE: EVALUATING IMMUNE CHECKPOINT INHIBITION IN SOLID TUMOR PATIENTS WITH HOMOLOGOUS RECOMBINATION REPAIR DEFICIENCY

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SIGNATURE PAGE

The signature below constitutes the approval of this protocol and the attachments and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines.

Principal Investigator:

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Name: _____

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{Include signature blocks for Clinical Site Investigator(s), when applicable. Duplicate as needed}

Clinical Site Investigator:

Signed: _____ Date: _____

Name: _____

Title: _____

1.0 TRIAL SUMMARY

Abbreviated Title	Pembrolizumab activity in patients with HR competent and deficient tumors
Trial Phase	II
Clinical Indication	Solid Tumors
Trial Type	Therapeutic
Type of control	None
Route of administration	Intravenous
Trial Blinding	None
Treatment Groups	One with stratification
Number of trial subjects	32-50
Estimated enrollment period	1 year
Estimated duration of trial	2 years
Duration of Participation	Until tumor progression
Estimated average length of treatment per patient	6 months

2.0 TRIAL DESIGN

Phase II trial in which patients with metastatic solid tumors experiencing progression after first line standard chemotherapy or for which there is no standard chemotherapy, and for which pembrolizumab does not have an FDA or compendia listing approved indication, will receive pembrolizumab intravenously at a dose of 200 mg every 3 weeks.

The end points are the immune-related objective response rate (primary) and the 20-week immune-related progression-free survival rate (secondary). Availability of paraffin embedded tumor material and willingness to provide blood for plasma DNA mutational analysis will be required for enrollment, as well as standard acceptable organ function and no history of autoimmune disease or previous treatment with immune check-point inhibitors. CT assessment at baseline and after every 8 weeks will be obtained to measure immune-related objective response rates. Patients will continue treatment until tumor progression or intolerable toxicity.

Stratification based on FANCD2 foci formation in tumor material (see below) to evaluate potential differences in activity will be performed. Exploratory correlatives include evaluation of mutation load on tumor and cell free DNA analysis and of gut microbiome composition on fecal samples.

3.0 OBJECTIVES & HYPOTHESES

3.1 Hypotheses

1. The immune checkpoint inhibitor pembrolizumab has clinically meaningful antitumor activity in solid tumor patients with functional deficiency in the Fanconi Anemia (FA) pathway in their tumors.

2. The Fanconi Anemia Triple Stain Inmmunofluorescence (FATSI) assay through detecting the lack of repair foci formation in the nucleus of proliferating cells will be able to identify these patients, and a FATSI negative assay will be associated with a better rate of responses than FATSI positive tumors.

3.2 Primary Objective

To evaluate the Immune-Related Objective Response Rate (IR-ORR) achieved with pembrolizumab in patients with Fanconi Anemia Repair Pathway functionally competent and functionally deficient tumors

3.3 Secondary Objective

To evaluate immune-related progression-free rate at 20 weeks (irPFS) and Overall Survival (OS) achieved with pembrolizumab in patients with Fanconi Anemia Repair Pathway functionally competent and functionally deficient tumors.

3.4. Exploratory Objectives

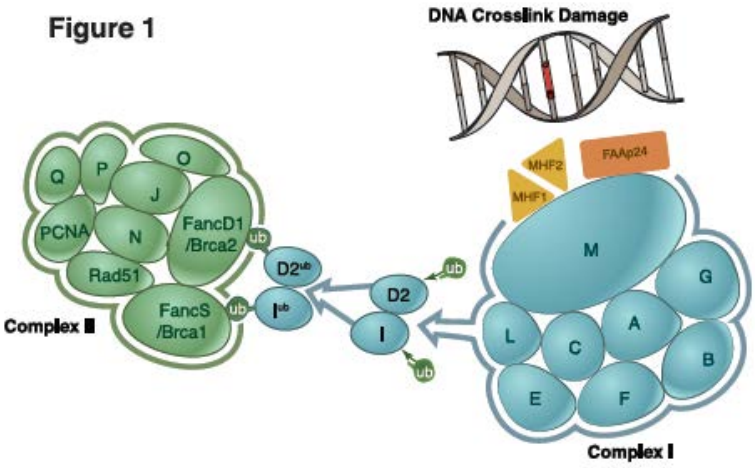
1. To evaluate mutation load and alterations in homologous recombination repair genes or other mechanisms of repair in blood specimens.

2. To evaluate gut microbiome composition of stool specimens in patients receiving pembrolizumab in this trial.

4.0 BACKGROUND & RATIONALE

4.1. Homologous Recombination Repair as an Anticancer Target

Excitement has been generated following the identification of mutations on the BRCA genes as potential predictors of response to PARP inhibitors and recent clinical trials demonstrating antitumor activity with PARP inhibitors in cancer patients with germline BRCA deficiency [1-5]. The rationale behind these observations is that the BRCA genes are involved in homologous recombination (HR), an example of double-strand break repair, and patients with inherited BRCA germline heterozygocity who developed cancer had acquired BRCA homozygous deficiency in their tumors. The resulting genetic instability becomes an advantage for the tumor to perpetuate. Targeting an additional repair pathway, such as base excision repair through PARP inhibition would induce inability for the tumor to survive, an example of a concept commonly called synthetic lethality.



The BRCA genes collaborate with several others in the Fanconi Anemia (FA) HR pathway [6-15]. Seventeen complementation groups/genes plus other interactive proteins have been described. Monoubiquitination of FancD2 and FancI by an FA core complex followed by nuclear co-localization with other DNA damage response proteins result in the formation of nuclear repair foci, thus foci formation is the focal functional output of this pathway (Fig 1). Based on this, we developed an immunofluorescence based method, FancD2/DAPI/Ki67 (Fanconi Anemia Triple Stain Immunofluorescence - FATSI), which permits the observation of FancD2 foci formation (or lack thereof) in the nucleus of proliferating cells in paraffin embedded tumor tissues [16], and screened >600 patients in a clinical trial for foci formation deficiency (Table 1) [17]. Functional deficiency was found in 29% of solid tumor patients. We also developed a targeted FA sequencing panel to evaluate potential genetic defects resulting in FA functional deficiency in our patients, and confirmed the ability of the FATSI test to enrich for patients exhibiting these alterations at the genomic level.

Table 1. Tissue screening results

Primary tumor type	FATSI negative	FATSI positive	Patients tested	% FATSI negative
Colon	63	104	167	37.7
Rectal	5	9	14	35.7
Breast	41	101	142	28.8
Lung non–small cell	19	78	97	19.6
Lung small cell	6	25	31	19.4
Ovarian	6	20	26	23.1
Biliary track	8	13	21	38.1
Pancreatic	3	17	20	15.0
Bladder	5	13	18	27.8
Head & neck	6	12	18	33.3
Endometrium	1	12	13	7.7
Prostate	1	12	13	7.7
Adenoca unknown primary	2	8	10	20.0
Neuroendocrine	3	6	9	33.3
Mesothelioma	2	5	7	28.6
Cervical	0	5	5	0
Thymic	2	3	5	40.0
Sarcoma	1	2	3	33.3
Melanoma	2	1	3	66.7
Gastro-intestinal stromal tumor	1	2	3	33.3
Stomach	1	2	3	33.3
Small bowell	2	1	3	66.7
Appendix	1	1	2	50.0
Renal	1	1	2	50.0
Adrenal	1	1	2	50.0
Testicular	1	0	1	100.0
Vulva	0	1	1	0
Penile	0	1	1	0
Fallopian	0	1	1	0
Peritoneal	1	0	1	100.0
Hepatic	0	1	1	0
Total	185	458	643	28.7

We also showed that it is safe to administer the PARP inhibitor veliparib at doses up to 300 mg per day to patients with FA deficient tumors, and that veliparib can be safely combined with the DNA damaging agent mitomycin C. Activity was seen for the combination in heavily pretreated patients [17]. However, veliparib as a single agent, outside of BRCA/RAD51 germline mutated breast cancer did not show a substantial level of clinical activity. Potential reasons for this discrepancy would include: 1- veliparib is a weak PARP-trapping agent [18,19]; 2- restoration of FA functionality as a result of systemic treatment received between the time of tissue collection and enrollment in the trial [20-23]; or 3- the presence of additional mutations to which the repair deficient cell has become addicted (non-oncogenic addiction/induced-essentiality) [24-25].

4.2 Immune Checkpoint Inhibition as a Therapeutic Strategy

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

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

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

Pembrolizumab is a potent and highly selective humanized monoclonal antibody (mAb) of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Keytruda™ (pembrolizumab) is indicated for the treatment of patients with unresectable or metastatic melanoma; for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have high PD-L1 expression [Tumor Proportion Score (TPS) ≥ 50%)] as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations; for the treatment of patients with metastatic NSCLC whose tumors express PD-L1 (TPS ≥ 1%) as determined by an FDA-approved test, with disease progression on or after platinum-containing chemotherapy; for the treatment of patients with recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) with disease progression on or after platinum-containing chemotherapy based on tumor response rate and durability of response; and for the treatment of adult and pediatric patients with refractory classical Hodgkin lymphoma, or who have relapsed after 3 or more prior lines of therapy. Accelerated approval contingent on verification and description of clinical benefit in confirmatory trials was granted for the last two indications.

4.3 Preclinical and Clinical Trial Data for Pembrolizumab

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

4.4 The Interplay between DNA repair deficiency and Immune Checkpoint inhibition.

Le et al. recently reported a phase 2 study evaluating the clinical activity of pembrolizumab, in 41 patients with progressive metastatic carcinoma with or without mismatch-repair deficiency (26). The immune-related objective response rate and immune-related progression-free survival rate were 40% (4 of 10 patients) and 78% (7 of 9 patients), respectively, for mismatch repair-deficient colorectal cancers and 0% (0 of 18 patients) and 11% (2 of 18 patients) for mismatch repair-proficient colorectal cancers. The median progression-free survival and overall survival were not reached in the cohort with mismatch repair-deficient colorectal cancer but were 2.2 and 5.0 months, respectively, in the cohort with mismatch repair-proficient colorectal cancer.

Interestingly, patients with mismatch repair-deficient non-colorectal cancer had responses similar to those of patients with mismatch repair-deficient colorectal cancer (immune-related objective response rate, 71% [5 of 7 patients]; immune-related progression-free survival rate, 67% [4 of 6 patients]). Whole-exome sequencing revealed a mean of 1782 somatic mutations per tumor in mismatch repair-deficient tumors, as compared with 73 in mismatch repair-proficient tumors (P=0.007), and high somatic mutation loads were associated with prolonged progression-free survival (P=0.02). Since somatic mutations have the potential to encode "non-

self" immunogenic antigens the authors hypothesized that tumors with a large number of somatic mutations due to mismatch-repair defects may be susceptible to immune checkpoint blockade.

5.0 RATIONALE

5.1 Rationale for the Trial and Selected Subject Population

Following the logic behind the sensitivity of patients with mismatch repair-deficient tumors to pembrolizumab, tumors with other type of repair deficiency, such as homologous recombination repair would plausibly have a large number of somatic mutations and likely be susceptible to immune checkpoint blockade. FATSI, given its ability to differentiate between functionally deficient and functionally competent Fanconi Anemia pathway tumors could identify additional patients susceptible to pembrolizumab.

Rather than patient pre-selection, a design that incorporates all comers (repair competent and deficient) with a stratification approach would be more suitable for preliminary evaluation of this concept. This approach is consistent with the evaluation by Le et al. for mismatch repair discussed above.

5.2 Rationale for Pembrolizumab Dose Selection/Regimen

An open-label Phase I trial (Protocol 001) evaluated the safety and clinical activity of single agent pembrolizumab. The dose escalation portion of this trial evaluated three dose levels, 1 mg/kg, 3 mg/kg, and 10 mg/kg, administered every 2 weeks (Q2W) in subjects with advanced solid tumors. All three dose levels were well tolerated and no dose-limiting toxicities were observed. This first in human study of pembrolizumab showed evidence of target engagement and objective evidence of tumor size reduction at all dose levels (1 mg/kg, 3 mg/kg and 10 mg/kg Q2W). No MTD was identified. PK data analysis of pembrolizumab administered Q2W and Q3W showed slow systemic clearance, limited volume of distribution, and a long half-life (refer to IB). Pharmacodynamic data (IL-2 release assay) suggested that peripheral target engagement is durable (>21 days).

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

It is also assumed that the dynamics of pembrolizumab target engagement will not vary meaningfully with tumor type.

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

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

5.3.Rationale for Endpoints

5.3.1 Efficacy Endpoints

The primary efficacy endpoint is overall Immune-Related Objective Response Rate (IR-ORR).

Secondary efficacy endpoints will include Progression Free Survival (PFS) and Overall Survival (OS).

We expect that pembrolizumab will have a higher clinically meaningful antitumor activity, as measured by IR-ORR and PFS in patients with solid tumors with functional deficiency in the Fanconi Anemia (FA) pathway, compared to those with functionally competent repair.

Based on our prior screening data, we anticipate that close to 30% of patients with solid tumors, depending on tumor type will be FA functionally deficient and that the response rate in these patients will be very similar than what was seen for patients with mismatch repair deficient colorectal cancer. The latter will not be included in this trial as we are trying to identifying another subset of highly responsive patients.

5.3.2 Biomarker Research and Correlative Endpoints

FATSI Assessment. The main hypothesis of this trial is that pembrolizumab has clinically meaningful antitumor activity in solid tumor patients with functional deficiency in the Fanconi Anemia (FA) pathway in their tumors. We will be performing The FATSI assay, as previously described [16,17], in archived paraffin embedded tumors of enrolled patients to assess for functional deficiency. We hypothesize that a FATSI negative assay will be associated with a better response rate, that those patients able to form FANCD2 repair foci. However, we will not preselect patients to this trial based on FATSI negativity.. The non-selection approach will avoid bias in case we observe a higher than expected rate of antitumor response or PFS in our treated patients independent of FATSI status. The results will be exploratory in nature, as there will not be sufficient statistical power (see Statistics Section).

Tissue and Blood DNA sequencing. We will obtain a blood sample at the beginning of the trial, prior to pembrolizumab therapy in participating patients in order to obtain cell free DNA for mutation analysis, and will also perform tumor DNA sequencing in archival tissue material in an attempt to search for the gene abnormalities responsible for the FA functional deficiency when relevant, as well as an estimation in mutation load. We will refer for family genetic counseling those patients for which germline deficiency is a consideration, either by family history or by results of the above tests. The correlative methods to be utilized are not validated for germline mutation and cancer risk analysis, but whenever a consideration is raised by results genetic counseling with validation analysis is the best ethical approach.

Microbiome Exploratory Evaluation. It has been suggested that alterations in the interactions between gut microbiota and host immunity can influence the outcome of cancer immunotherapy [27,28]. For example, in several preclinical cancer models tumor progression was controlled by antibodies against CTLA-4 in specific pathogen free but not in germ free mice. Moreover, a combination of broad-spectrum antibiotics compromised the antitumor effects of CTLA-4–specific antibodies. In germ free or antibiotic-treated mice, activation of splenic effector $CD4^+$ T cells and tumor-infiltrating lymphocytes (TILs) induced by antibody against CTLA-4 was significantly decreased. Restoration of CTLA-4 antibody activity was associated with oral feeding of specific pathogen isolates, compared to others. [27].

In patients with melanoma, ipilimumab treatment led to changes in the composition of the microbiome and fecal transplants composed of different microbiomes based on a clustering algorithm from these patients to tumor bearing mice identified sizeable differences in response to CTLA-4 blockade. Hence, ipilimumab can modify the abundance of immunogenic *Bacteroides* spp. in the gut, which in turn affects its anticancer efficacy [27].

Similarly, melanoma growth in mice harboring distinct commensal microbiota had differences in spontaneous antitumor immunity, which were eliminated upon cohousing or after fecal transfer. Sequencing of the 16S ribosomal RNA identified Bifidobacterium as associated with the antitumor effects. Oral administration of Bifidobacterium alone improved tumor control to the same degree as programmed cell death protein 1 ligand 1 (PD-L1)–specific antibody therapy, and combination treatment nearly abolished tumor outgrowth. Augmented dendritic cell function leading to enhanced CD8+ T cell priming and accumulation in the tumor microenvironment mediated the effect [28].

Not only associations of specific microbiomes with antitumor activity of immune checkpoint inhibitors merit considerations, but also potentially toxicity. A prospective study of patients with metastatic melanoma undergoing ipilimumab treatment demonstrated that increased representation of bacteria belonging to the Bacteroidetes phylum correlated with resistance to the development of checkpoint-blockade-induced colitis [29].

The evidence also suggests that it is not enough to look at the microbial profile of the subject, but there is a need to understand what genes are expressed by the microbial community, what metabolites are released by the microbiome as well as the host as a result of their interaction, and how the host genes and markers play a role in this complex web of interactions. If some therapies are working well (or poorly) on select patients, it is critical to understand the role of the microbiome in this process so that therapies can be improved, augmented, and better

targeted to individual patients. We choose to pick the three most important "omics" data sets to generate for the subject cohort, i.e., microbiome, metatranscriptome and metabolome.

We will gather data in gut pathogens from fecal samples from patients in this trial. Our unique population (65% Hispanics with different ages at immigration to the USA) may offer valuable preliminary data of potential associations to be tested in future studies as we anticipate clear diversity in the microbiome of these patients, as its composition is likely influenced by geography and culture.

6.0 METHODOLOGY

6.1 Entry Criteria

Diagnosis/Condition for Entry into the Trial

Patients with metastatic or recurrent solid malignancy who have progressed on first line standard of care treatment or for which defined standard of care does not exist. Patients for which pembrolizumab has an FDA approved indication and for whom pembrolizumab is covered by their insurance should receive standard commercial pembrolizumab and will not be eligible for this trial.

Subject Inclusion Criteria

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

1. Be willing and able to provide written informed consent/assent for the trial.

2. Be ≥ 18 years of age on day of signing informed consent.

3. Have measurable disease based on RECIST 1.1.

4. Be willing to provide consent for retrieval of archival tumor material tissue from a previously obtained core or excisional biopsy of a tumor lesion. Consent will also be given to obtain tumor material from any new biopsy or excision planned for standard of care during active participation in this trial or when documenting first tumor progression after pembrolizumab treatment.

5. Have a performance status of 0, 1 or 2 on the ECOG Performance Scale.

6. Have a tumor presentation at screening for which pembrolizumab does not have an FDA approved indication for commercial use (see Section 4.2). Those patients for which insurance is not available, or insurance denies pembrolizumab will be considered in a case by case basis.

7. Demonstrate adequate organ function as defined in Table 2, all screening labs should be performed within 15 days of treatment initiation.

Table 2. Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1,500 /mcL
Platelets	≥100,000 / mcL
Hemoglobin	≥9 g/dL or ≥5.6 mmol/L without transfusion or EPO dependency (within 7 days of assessment)
Renal	
Serum creatinine **OR** Measured or calculated[a] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 X upper limit of normal (ULN) **OR** ≥60 mL/min for subject with creatinine levels > 1.5 X institutional ULN
Hepatic	
Serum total bilirubin	≤ 1.5 X ULN **OR**
	Direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 X ULN **OR** ≤ 5 X ULN for subjects with liver metastases
Albumin	≥2.5 mg/dL
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT) Activated Partial Thromboplastin Time (aPTT)	≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants ≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
[a]Creatinine clearance should be calculated per institutional standard.	

8. Female subject of childbearing potential should have a negative urine or serum pregnancy within 72 hours prior to receiving the first dose of study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

9. Female subjects of childbearing potential (Section 5.7.2) must be willing to use an adequate method of contraception as outlined in Section 5.7.2 – Contraception, for the course of the study through 120 days after the last dose of study medication.

10. Male subjects of childbearing potential (Section 5.7.1) must agree to use an adequate method of contraception as outlined in Section 5.7.1- Contraception, starting with the first dose of study therapy through 120 days after the last dose of study therapy.

Note: For 9 and 10, abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject.

6.1.1 Expansion Cohort.

Ten (10) additional subjects with the diagnosis of metastatic or recurrent endometrial carcinoma will be enrolled in the trial at the conclusion of regular enrollment with subject with the eligibility discussed in 6.1., and as per Sample size Calculation and Statistics Section (Section 12). The following will be necessary criteria for this expansion cohort.

1. Diagnosis of Endometrial Carcinoma or Sarcoma which is metastatic and has failed standard treatment or is recurrent, or for which standard chemotherapy is contraindicated or refused by patient.

2. Sufficient tissue is available for correlative studies as specified on Section 9.0.2.8.

3. MSI studies have been performed, either by immunohistochemistry or next generation sequencing and results show that patient is MS low or stable.

4. Patient meet all the inclusion criteria discussed above on 6.1 and none of the exclusion criteria discussed below on section 6.2.

6.2 Subject Exclusion Criteria

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

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

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

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

4. Hypersensitivity to pembrolizumab or any of its excipients.

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

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

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

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

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

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

9. Has active autoimmune disease that has required systemic treatment in the past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.

10. Has immunohistochemically proven mismatch repair deficient cancer (this test is standard in our center for colorectal and endometrial cancer patients, and documentation will be required to be negative to accept outside referrals with colorectal or endometrial cancer for this trial).

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

12. Evidence of interstitial lung disease.

13. Has an active infection requiring systemic therapy.

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

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

16. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the pre-screening or screening visit through 120 days after the last dose of trial treatment.

17. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent.

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

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

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

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

6.3 Trial Treatments

The treatment to be used in this trial is outlined below in Table 3.

Table 3. Trial Treatment

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/ Treatment Period	Use
Pembrolizumab	200 mg	Q3W	IV infusion	Day 1 of each 3 week cycle	Experimental

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

6.4 Dose Selection/Modification

Dose Selection

The rationale for selection of doses to be used in this trial is provided in Section 4.0 – Background and Rationale. Details on preparation and administration of pembrolizumab (MK-3475) are provided in the Package Insert.

Dose Modification (Escalation/Titration/Other)

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 4 below. See Section 6.8.1 for supportive care guidelines, including use of corticosteroids.

Table 4. Dose Modification and Toxicity Management Guidelines for Immune-related AEs Associated with Pembrolizumab

General instructions:

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

Immune-related AEs	Toxicity grade or conditions (CTCAEv4.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment • Add prophylactic antibiotics for opportunistic infections
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus). • Participants with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
	Grade 4	Permanently discontinue		
AST / ALT elevation or Increased bilirubin	Grade 2	Withhold	• Administer corticosteroids (initial dose of 0.5-1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable
	Grade 3 or 4	Permanently discontinue	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	

Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold	• Initiate insulin replacement therapy for participants with T1DM • Administer anti-hyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes.
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated.	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hyperthyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hypothyroidism	Grade 2-4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyroinine) per standard of care	• Monitor for signs and symptoms of thyroid disorders.
Nephritis and Renal dysfunction	Grade 2	Withhold	• Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper.	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1 or 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
All other immune-related AEs	Intolerable/ persistent Grade 2	Withhold	• Based on type and severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3	Withhold or discontinue based on the type of event. Events that require discontinuation include and not limited to: Gullain-Barre Syndrome, encephalitis		

	Grade 4 or recurrent Grade 3	Permanently discontinue		
1. Withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician. **NOTE:** For participants with Grade 3 or 4 immune-related endocrinopathy where withhold of pembrolizumab is required, pembrolizumab may be resumed when AE resolves to ≤ Grade 2 and is controlled with hormonal replacement therapy or achieved metabolic control (in case of T1DM).				

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

6.5 Timing of Dose Administration

Trial treatment should be administered on Day 1 of each cycle after all procedures/assessments have been completed as detailed on the Trial Flow Chart (Section 8.0). Trial treatment may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons.

All trial treatments will be administered on an outpatient basis.

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

The Package Insert contains specific instructions for the preparation of the pembrolizumab infusion fluid and administration of infusion solution.

6.6 Trial Blinding/Masking

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

6.7 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.

6.7.1 Acceptable Concomitant Medications

All treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the case report form (CRF) including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the case report form (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 11.

6.7.2 Prohibited Concomitant Medications

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

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

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.

6.8 Rescue Medications & Supportive Care

6.8.1 Supportive Care Guidelines

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

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

It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event.

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

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

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

- **Type 1 diabetes mellitus (if new onset, including diabetic ketoacidosis [DKA]) or ≥ Grade 3 Hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis (DKA)**
  - For **T1DM** or **Grade 3-4** Hyperglycemia
  - Insulin replacement therapy is recommended for Type I diabetes mellitus and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria.
  - Evaluate patients with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.
- **Hypophysitis**:
  - For **Grade 2** events, treat with corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
  - For **Grade 3-4** events, treat with an initial dose of IV corticosteroids followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
- **Hyperthyroidism or Hypothyroidism**:

  Thyroid disorders can occur at any time during treatment. Monitor patients for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders.

  - **Grade 2** hyperthyroidism events (and **Grade 2-4** hypothyroidism):
  - In hyperthyroidism, non-selective beta-blockers (e.g. propranolol) are suggested as initial therapy.
  - In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyroinine, is indicated per standard of care.
  - **Grade 3-4** hyperthyroidism
  - Treat with an initial dose of IV corticosteroid followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
- **Hepatic**:
  - For **Grade 2** events, monitor liver function tests more frequently until returned to baseline values (consider weekly).
  - Treat with IV or oral corticosteroids
  - For **Grade 3-4** events, treat with intravenous corticosteroids for 24 to 48 hours.
  - When symptoms improve to Grade 1 or less, a steroid taper should be started and continued over no less than 4 weeks.

- **Renal Failure or Nephritis**:
  - For **Grade 2** events, treat with corticosteroids.
  - For **Grade 3-4** events, treat with systemic corticosteroids.
  - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
- **Management of Infusion Reactions**: Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Table 5 below shows treatment guidelines for subjects who experience an infusion reaction associated with administration of pembrolizumab (MK-3475).

Table 5. Infusion Reaction Treatment Guidelines

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

6.9 Diet/Activity/Other Considerations

6.9.1 Diet

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

6.9.2 Contraception

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

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

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

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

OR

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

OR

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

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

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

OR

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

Acceptable methods of contraception are[‡]:

Single method (one of the following is acceptable):

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

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

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

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

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

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

6.9.3 Use in Pregnancy

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

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

6.9.4 Use in Nursing Women

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

7.0 SUBJECT WITHDRAWAL/DISCONTINUATION CRITERIA

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

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

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

The End of Treatment and Follow-up visit procedures are listed in Section 8 (Protocol Flow Chart) and Section 10.0.1 (Visit Requirements). After the end of treatment, each subject will be followed for 30 days for adverse event monitoring (serious adverse events will be collected for 90 days after the end of treatment). Subjects who discontinue for reasons other than progressive disease will have post-treatment follow-up for disease status until disease progression, initiating a non-study cancer treatment, withdrawing consent or becoming lost to follow-up. After documented disease progression each subject will be followed by telephone for overall survival until death, withdrawal of consent, or the end of the study, whichever occurs first.

7.1 Discontinuation of Study Therapy after CR

Discontinuation of treatment may be considered for subjects who have attained a confirmed CR that have been treated for at least 24 weeks with pembrolizumab and had at least two treatments with pembrolizumab beyond the date when the initial CR was declared.

7.2 Subject Replacement Strategy

We anticipate enrollment of 39 patients for which tumor and toxicity assessments following pembrolizumab administration can be made. We will replace patients enrolled for which clinical trial discontinuation was performed prior to any administration of pembrolizumab or those for which pembrolizumab is discontinued due to acute hypersensitivity reactions during the first administration of pembolizumab. An attempt will be made to assess tumor response in all enrolled patients as specified in the protocol. However, patients experiencing clinical deterioration after two doses of pembrolizumab, will be considered treatment failures and will count as tumor progression. These patients will not be replaced.

We are also expecting that 30% of the patients enrolled will be negative on the FATSI assay, which will be conducted in batched analyses.

See section 6.1.1 and 12.0.1 for expansion cohort.

7.3 Clinical Criteria for Early Trial Termination

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

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

2. Poor adherence to protocol and regulatory requirements

3. Incidence or severity of new adverse pembrolizumab drug reaction as reported by MERCK to the FDA indicates a potential health hazard to subjects and lead to modification in the drug labeling. The trial could be re-open following the adoption of required modifications in administration.

8 TRIAL FLOW CHART

8.1 Table 6. Study Flow Chart

Trial Period:	Screening	Treatment Cycles								End of Treatment		Post-Treatment	
Treatment Cycle/Title:	Main Study Screening	1	2	3	4	To be repeated beyond 8 cycles 5	6	7	8	Discon	Safety Follow-up	Follow Up Visits[b]	Survival Follow-Up
Scheduling Window (Days):	-21 to -1		± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days post discon	Every 8 weeks post discon	Every 12 weeks
Informed Consent	X												
Inclusion/Exclusion Criteria	X												
Demographics and Medical History	X	X	X	X	X	X	X	X	X				
Prior and Concomitant Medication Review	X	X	X	X	X	X	X	X	X				
Trial Treatment Administration		X	X	X	X	X	X	X	X				
Post-study anticancer therapy status											X	X	
Survival Status											X	X	X
Review Adverse Events		X	X	X	X	X	X	X	X	X			
Full Physical Examination	X												
Directed Physical Examination		X	X	X	X	X	X	X	X	X			
Vital Signs and Weight	X	X	X	X	X	X	X	X	X	X			
ECOG Performance Status	X	X	X	X	X	X	X	X	X	X			
Pregnancy Test – Urine or Serum β-HCG	X[c]												
PT/INR and aPTT	X[a]												
CBC with Differential	X[a]	X[b]	X	X	X	X	X	X	X				
Comprehensive Serum Chemistry Panel (see Table 9 for lab details)	X[a]	X[b]	X	X	X	X	X	X	X				
Urinalysis	X[a]												
T3, FT4 and TSH	X[a]			X			X						

Efficacy Measurements													
Tumor Imaging	X			X			X[d]			X			
Archival Tissue Collection/Correlative Studies Blood													
Archival or Newly Obtained Tissue Collection	X												
Correlative Studies Blood Collection See Protocol Lab Manual.	X	X	X	X						X			

[a] Must be performed within 10 days of the first treatment visit (Cycle 1 Day 1).
[b] Hematology (CBC with differential) and Creatinine results must be available and reviewed by the Investigator prior to infusion. A spot creatinine result may be used to proceed with treatment, as Chemistry results may not be available.
[c] Must be performed within 72 hours of the first treatment visit (Cycle 1 Day 1).
[d] Tumor imaging will only be required every 12 weeks for patients that have been on treatment for more than 1 year.

9.0 TRIAL PROCEDURES

The Trial Flow Chart - Section 8.0 summarizes the trial procedures to be performed at each visit. Individual trial procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator.

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

9.0.1 Administrative Procedures

9.0.1.1 Informed Consent

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

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

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

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

Specifics about a trial and the trial population will be added to the consent form template at the protocol level.

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

9.0.1.2 Inclusion/Exclusion Criteria

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

9.0.1.3 Medical History

A medical history will be obtained by the investigator or qualified designee. Medical history will include all active conditions, and any condition diagnosed within the prior 10 years that are considered to be clinically significant by the Investigator. Details regarding the disease for

which the subject has enrolled in this study will be recorded separately and not listed as medical history.

9.0.1.4 Prior and Concomitant Medications Review

9.0.1.4.1 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 21 days before starting the trial. Treatment for the disease for which the subject has enrolled in this study will be recorded separately and not listed as a prior medication.

9.0.1.4.2 Concomitant Medications
The investigator or qualified designee will record medication, if any, taken by the subject during the trial. All medications related to reportable SAEs and ECIs should be recorded as defined in Section 9.2.

9.0.1.5 Disease Details and Treatments

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

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

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

9.0.2 Clinical Procedures/Assessments

9.0.2.1 Adverse Event (AE) Monitoring
The investigator or qualified designee will assess each subject to evaluate for potential new or worsening AEs as specified in the Trial Flow Chart and more frequently if clinically indicated. Adverse experiences will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE Version 4.0 (see Section 11.2). Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

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

9.0.2.3 Directed Physical Exam

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

9.0.2.4 Vital Signs

The investigator or qualified designee will take vital signs at screening, prior to the administration of each dose of trial treatment and at treatment discontinuation as specified in the Trial Flow Chart (Section 8). Vital signs should include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at screening only.

9.0.2.5 Eastern Cooperative Oncology Group (ECOG) Performance Scale

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

9.0.2.6 Tumor Imaging and Assessment of Disease

Tumor assessments will be performed by computer tomography (CT) or Magnetic Resonance Imaging (MRI). Measurable disease will be required by computer tomography or MRI examination obtained within 21 days of first dose of therapy. Scans obtained prior to consenting will be allowed, as long as performed within 21 days of study initiation. CT Scans or MRI's will be repeated every 2 cycles (3 weeks cycles); that is before every third dose of pembrolizumab in order to assess response to therapy. Tumor imaging will only be required every 12 weeks for patients that have been on treatment for more than 1 year. Immune-related Response Criteria (irRC) [30] will be utilized for assessment of response to therapy.
Systematic criteria designated immune-related response criteria were defined based on four distinct response patterns seen after administration of ipilumimab: (a) shrinkage in baseline lesions, without new lesions; (b) durable stable disease (in some patients followed by a slow, steady decline in total tumor burden); (c) response after an increase in total tumor burden; and (d) response in the presence of new lesions. These four patterns were associated with favorable survival [30].

For the irRC index and measurable new lesions are taken into account to calculate evolving tumor burden. At baseline, the sum of the products of the two largest perpendicular diameters (SPD) of all index lesions (five lesions per organ, up to 10 visceral lesions) is calculated. At each subsequent tumor assessment, the SPD of the index lesions and of new, measurable lesions (up to 5 new lesions per organ; 10 visceral lesions) are added together to provide the total tumor burden. A comparison of the use of SPD in WHO criteria versus the use of tumor burden in irRC is presented in Table 8.

Table 7. Comparison between WHO criteria and the irRC

	WHO	irRC
New, measurable lesions	Always represent PD	Incorporated into tumor burden.
New, nonmeasurable lesions	Always represent PD	Do not define progression (but preclude irCR)

Non-index lesions	Changes contribute to defining best overall response	Contribute to defining irCR (complete disappearance required)
CR	Disappearance of all lesions in two consecutive observations not less than 4 weeks apart.	Disappearance of all lesions in two consecutive observations not less than 4 weeks apart.
PR	≥50% decrease in SPD compared with baseline in two observations at least 4 weeks apart, in absence of new lesions or inequivocal progression of non-index lesions.	≥50% decrease in tumor burden compared with baseline in two observations at least 4 weeks apart.
SD	50% decrease in SPD compared to baseline cannot be established nor 25% increase compared with nadir, in absence of new lesions or inequivocal progression of non-index lesions.	50% decrease in tumor burden compared with baseline cannot be established nor 25% increase compared with nadir.
PD	At least 25% increase in SPD compared with nadir and/or unequivocal progression of non-index lesions and/or appearance of new lesions (at any single time point).	At least 25% increase in tumor burden compared with nadir (at any single time point) in two consecutive observations at least 4 weeks apart.

9.0.2.7 Overall response using the irRC

- **irCR**: Complete disappearance of all lesions (whether measurable or not, and no new lesions) confirmed by a repeat, consecutive assessment no less than 4 weeks from the date first documented.

- **Ir PR**: Decrease in tumor burden ≥50% relative to baseline confirmed by a consecutive assessment at least 4 weeks after first documentation.

- **irSD**: Not meeting criteria for irCR or irPR, in absence of irPD.

- **irPD**: Increase in tumor burden ≥25% relative to nadir (minimum recorded tumor burden) confirmed by a repeat, consecutive assessment no less than 4 weeks from the date first documented.

Major differences with other tumor response criteria include: PR or SD in the presence of new lesions, as long as they met the respective threshold of response based on total differences in tumor burden; an SD does not require confirmation; however PD requires confirmation by another scan at least 4 weeks apart in the absence of rapid clinical deterioration.

9.0.2.8 Tumor Tissue Collection and Correlative Studies Sampling

We will evaluate functionality of the Fanconi Anemia pathway in patient tumor samples. Formalin fixed paraffin embedded (FFPE) will be obtained from patients participating in the trial. The presence of archival tumor material is part of the criteria for eligibility for this trial. FFPE tumor tissue will be cut at 4 microns, placed on positively charged slides and stained

with hematoxylin and eosin (HE). Additional sections for FATSI staining will be placed in a 60°C oven for 1 h, cooled, deparaffinized and rehydrated through xylenes and graded ethanol solutions to water in standard fashion. Antigen retrieval will be performed by placing slides in Dako's TRS (pH 6.1) antigen retrieval solution (Dako, Carpenteria, CA) in a calibrated vegetable steamer (Black and Decker). Slides then will be placed on a Dako Autostainer for automated staining. The tissue sections will be incubated with a primary antibody cocktail of rabbit polyclonal FANC-D2 antibody at a dilution of 1:1000 and a monoclonal anti-Ki67 mouse antibody at a dilution of 1: 150, and incubated for 1 hour at room temperature. Sections then will be co-incubated with a secondary antibody (FITC conjugated to anti-rabbit IgG and Alexafluor 594 donkey anti-mouse) at 1:1000 and incubated for 1 hour at room temperature. All rinses will be performed on the autostainer with TBST. The sections will be mounted on glass slides using a 4' 6-diamidino-2-phenylindole (DAPI)–containing embedding medium (Vysis Dapi 1, Abbott Laboratories, Downers Grove, IL). FANCD2 foci positive and negative cell lines (MCF-7 and PD20 cells) used as controls will be included on the sample slide during the procedure. The slides will be analyzed under a Nikon E-400 fluorescence microscope.

Circulating cell-free tumor DNA (ctDNA) carries comprehensive, inherently specific, and highly sensitive information. Studies in melanoma, breast, ovarian, and colon cancers have validated the potential applications of ctDNA to monitor tumor burden dynamically and precisely during treatment process. A liquid biopsy based on ctDNA could capture the entire heterogeneity of the disease longitudinally as well as in real time. Blood samples collected from the patients will be sent to Florida International University (Duan's lab) for genomic analysis.

All analyses regarding the microbiome will be performed by the Narasimhan laboratory.

The four "omics" profiles mentioned above will be processed using integrative analysis techniques developed by the Narasimhan laboratory on the machines available to BioRG. In particular, the method of heterogeneous correlation networks will help identify groups of entities from different omics data that tend to occur together or avoid each other. Groups of entities from the metagenome, metatranscriptome, metabolome and patient transcriptome will help generate useful hypotheses for further investigations. Using the functional annotations of the genes, it is possible to determine which microbial taxa are responsible for the functional genes of interest that are most differentially expressed. The analysis will also implicate the most relevant human pathways of interest. Using the KEGG metabolic pathways database, it is possible to hypothesize which microbial taxa are responsible for the most differentially abundant metabolites.

9.0.2.9 Laboratory Procedures/Assessments

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

Table 8. Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Blood	Serum β-human chorionic gonadotropin†
Hemoglobin	Alkaline phosphatase	Glucose	(β-hCG)†
Platelet count	Alanine aminotransferase (ALT)	Protein	PT (INR)
WBC (total and differential)	Aspartate aminotransferase (AST)	Specific gravity	aPTT
Red Blood Cell Count	Lactate dehydrogenase (LDH)	Microscopic exam *(If abnormal*	Total thriiodothyronine (T3)
Absolute Neutrophil Count	Carbon Dioxide	results are noted)	Free tyroxine (T4)
Absolute Lymphocyte Count	*(CO_2 or bicarbonate)*	Urine pregnancy test †	Thyroid stimulating hormone (TSH)
	Uric Acid		
	Calcium		
	Chloride		Blood and stools for correlative studies
	Glucose		
	Phosphorus		
	Potassium		
	Sodium		
	Magnesium		
	Total Bilirubin		
	Direct Bilirubin *(If total bilirubin is elevated above the upper limit of normal)*		
	Total protein		
	Blood Urea Nitrogen		
† Perform on women of childbearing potential only. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required.			

10.0 Withdrawal/Discontinuation

When a subject discontinues/withdraws prior to trial completion, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation. Any adverse events, which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 11 - Assessing and Recording Adverse Events. Subjects who a) attain a CR or b) complete 24 months of treatment with pembrolizumab may discontinue treatment with the option of restarting treatment if they meet the criteria specified in Section 7.1. After discontinuing treatment following assessment of CR, these subjects should return to the site for a Safety Follow-up Visit (described in Section 10.0.1.0) and then proceed to the Follow-Up Period of the study (described in Section 10.0.1.1).

10.0.1 Visit Requirements

Visit requirements are outlined in Section 8.0 - Trial Flow Chart. Specific procedure-related details are provided above in Section 9 - Trial Procedures.

10.0.1.0 Safety Follow-Up Visit

The mandatory Safety Follow-Up Visit should be conducted approximately 30 days after the last dose of trial treatment or before the initiation of a new anti-cancer treatment, whichever comes first. All AEs that occur prior to the Safety Follow-Up Visit should be recorded. Subjects with an AE of Grade > 1 will be followed until the resolution of the AE to Grade 0-1 or until the beginning of a new anti-neoplastic therapy, whichever occurs first. SAEs that occur within 90 days of the end of treatment or before initiation of a new anti-cancer treatment should also be followed and recorded.

10.0.1.1 Follow-up Visits

Subjects who discontinue trial treatment for a reason other than disease progression will move into the Follow-Up Phase and should be assessed every 6 weeks (42 ± 7 days) by radiologic imaging to monitor disease status. After 1 year, the imaging time point will occur every 9 weeks (± 7 days). Every effort should be made to collect information regarding disease status until the start of new anti-neoplastic therapy, disease progression, death, or end of the study Information regarding post-study anti-neoplastic treatment will be collected if new treatment is initiated.

10.0.1.2 Survival Follow-up

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

11.0 ASSESSING AND RECORDING ADVERSE EVENTS

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any

unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of pembrolizumab is also an adverse event.

Progression of the cancer under study is not considered 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 investigator will make every attempt to follow all subjects with non-serious adverse events for outcome.

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

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

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

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

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

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

Although pregnancy and lactation are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them) that occurs during the trial.

Pregnancies and lactations 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.

Pregnancies and lactations that occur from the time of treatment allocation/randomization through 120 days following cessation of Sponsor's product, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, must be reported by the investigator. All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

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

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

11.0.3.1 Serious Adverse Events

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

- Results in death;
- Is life threatening;
- Results in persistent or significant disability/incapacity;
- Results in or prolongs an existing inpatient hospitalization;
- Is a congenital anomaly/birth defect;
- Is an other important medical event

- **Note:** In addition to the above criteria, adverse events meeting either of the below criteria, although not serious per ICH definition, are reportable to the Merck in the same timeframe as SAEs to meet certain local requirements. Therefore, these events are considered serious by Merck for collection purposes.
  - Is a new cancer (that is not a condition of the study);
  - Is associated with an overdose.

For the time period beginning when the consent form is signed until treatment allocation/randomization, any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study that occurs to any subject must be reported within 24 hours to the Sponsor 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 serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study, whether or not related to the Merck product, must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety.

Additionally, any serious adverse event, considered by an investigator who is a qualified physician to be related to Merck product that is brought to the attention of the investigator at any time following consent through the end of the specified safety follow-up period specified in the paragraph above, or at any time outside of the time period specified in the previous paragraph also must be reported immediately to the Sponsor and to Merck Global Safety.

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

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

A copy of all 15 Day Reports and Annual Progress Reports is submitted as required by FDA, Pharmaceutical and Medical Devices agency (PMDA) or other local regulators. Investigators will cross reference this submission according to local regulations to the Merck Investigational Compound Number (IND, CSA, etc.) at the time of submission. Additionally investigators will submit a copy of these reports to Merck & Co., Inc. (Attn: Worldwide Product Safety; FAX 215 993-1220) at the time of submission to FDA.

11.0.3.2 Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be reported within 24 hours to the Sponsor 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 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:

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

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

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

11.0.3.3 Protocol-Specific Exceptions to Serious Adverse Event Reporting.

Specifically, the suspected/actual events covered in this exception include any event that is disease progression of the cancer under study.

The Sponsor will monitor unblinded aggregated efficacy endpoint events and safety data to ensure the safety of the subjects in the trial. Any suspected endpoint which upon review is not progression of the cancer under study will be forwarded to Merck Global Safety as a SAE within 2 working days of determination that the event is not progression of the cancer under study

Hospitalization related to convenience (e.g.transportation issues etc.) will not be considered a SAE.

11.0.4 Evaluating Adverse Events

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

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

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

Table 9. 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-appropriate instrumental ADL.**
	Grade 3	**Severe or medically significant but not immediately life-threatening; hospitalization or prolongation or hospitalization indicated; disabling; limiting self-care ADL.**
	Grade 4	**Life threatening consequences; urgent intervention indicated.**
	Grade 5	**Death related to AE**
Seriousness	A serious adverse event is any adverse event occurring at any dose or during any use of Merck product that:	
	†**Results in death**; or	
	†**Is life threatening; or** places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred (Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.); or	
	†**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or	
	†**Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization 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 diagnosed prior to the use of a Merck product and is documented in the patient's medical history.); or	
	†**Is a congenital anomaly/birth defect** (in offspring of subject taking the product regardless of time to diagnosis);or	
	Is a new **cancer** (that is not a condition of the study) **(**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 requirements); **or**	
	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 the Sponsor and to Merck within 2 working days.	
	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	
Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units	
Action taken	Did the adverse event cause 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	
	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 pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
	Time Course	Did the AE follow in a reasonable temporal sequence from administration of Merck product? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?
	Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors

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

11.0.5 Sponsor Responsibility for Reporting Adverse Events

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

12.0 SAMPLE CALCULATION AND STATISTICAL ANALYSIS PLAN

The primary endpoint is overall immune-related objective response rate. We expect that similar to mismatch repair deficient patients, the immune-related objective response will be at or above 40% in patients with functional FA deficiency (FATSI negative), and less than 10% in patients without either homologous recombination repair deficiency or mismatch repair deficiency. Patients with mismatch repair deficiency will be excluded from this trial. Based on our prior screening data, we anticipate that close to 30% of patients with solid tumors, depending on tumor type will be FA functionally deficient.

We will utilize a two-stage phase II trial design to detect an iORR of at least 20% in the whole population tested vs. the null hypothesis that the true iORR is at most 5%, representing a response by chance alone, or other infrequent unknown mechanism. Specifically, we will test the null hypothesis H_0: iORR $\leq$ 5% vs. H_1: iORR $\geq$ 20% with 90% power and a Type I error rate of 10%. The alternative hypothesis of 20% iORR represents a weighted average of the anticipated 40% response in FATSI-negative patients and 10% response in FATSI-positive, assuming a 3 to 7 ratio of these patient groups. Interim analysis requires that at least two of the first 20 evaluable patients enrolled have an objective response. If this occurs, we will accrue 19 additional patients for a total of 39. Overall rejection criterion of the null hypothesis is observing at least 4 responses.

The proposed two-stage design was chosen instead of the Simon Optimal or Minimax design because it has a larger first stage enrollment and thus a higher expected number of FATSI-negative patients in the interim analysis. Total enrollment of 39 patients is only slightly greater than that of the Simon designs but has the advantage of increasing the expected number of FATSI-negative patients. Additionally, the proposed design has a higher early stopping probability under the null hypothesis. The following table summarizes these operating characteristics.

Table 10:

Design	First stage enrollment	Expected FATSI-patients, 1st stage	PET	Total enrollment	Total expected FATSI-patients	Actual α	Power	Expected study size
Optimal	12	4	0.54	37	11	0.093	90.2%	23
Minimax	18	5	0.40	32	10	0.072	90.1%	26
Proposed	**20**	**6**	**0.74**	**39**	**12**	**0.099**	**91.7%**	**25**

FATSI-: FATSI negative. **PET:** Probability of early termination at completion of first stage enrollment. **α:** Probability of false positive finding (type 1 error, falsely rejecting the null hypothesis).

We will analyze the paraffin embedded tumors of the participating patients for FA functional deficiency. Analysis will be conducted in batches.

We will report the 90% confidence interval estimates of iORR both overall and by FATSI status using the exact method (Clopper-Pearson). We note, however, that the planned study is too small for a well-powered comparison given that we expect only 12 FATSI-negative patients. Instead, variation in iORR by FATSI status will be assessed by considering the one-sided 95% lower confidence limit (95%LCL) for the difference. The following table illustrates the 95%LCL for several possible study outcomes in which iORR is higher in FATSI- patients. Taking the second rows as an example, an observed increase in iORR for FATSI-negative patients of 34.3%, based on 5 out of 12 FATSI- responders compared with 2 out of 27 FATSI+ responders, provides 95% confidence that the true increase for patients with FA deficient tumors is at least 9.4%, suggesting that further study of Pembrolizumab in FA deficient patients is warranted.

Table 11:

iORR					
FATSI–		FATSI+		Difference	95%LCL
5 / 12	41.7%	1/27	3.7%	38.0%	13.8%
5 / 12	41.7%	2/27	7.4%	34.3%	9.4%
5 / 12	41.7%	3/27	11.1%	30.6%	5.1%
4 / 12	33.3%	1/27	3.7%	29.6%	6.5%
4 / 12	33.3%	2/27	7.4%	25.9%	2.1%
4 / 12	33.3%	3/27	11.1%	22.2%	-2.3%

The incidence of severe (NCI CTCAE v4 grade 3+) adverse events or toxicities will be described. Kaplan-Meier curves will be used to estimate the distributions of overall survival and immune-related progression-free survival (iPFS). Point estimates and 2-sided 95% confidence intervals will be reported for selected times using Greenwood's variance and the log-log transform method. This will include the 20-week iPFS for purposes of comparison with the literature.

12.1 Expansion Cohort

At the conclusion of the accrual as specified above, an expanded cohort of 10 patients with the diagnosis of metastatic or recurrent endometrial carcinoma or endometrial sarcoma will be enrolled. These patients need tissue availability and documentation of microsatellite low or stable. (see Section 6.1.1 for inclusion/exclusion criteria). All clinical benefit measure parameters and correlatives will be obtained, as per the other patient. No additional statistical inferences, other than comparison between FATSI positives and negatives in terms of clinical outcome will be done.

12.2 Correlative Data

Additional correlative data other than FATSI status will be descriptive in nature and hypothesis generating. These include mutation load in tumor and cell free DNA, FA related gene mutations and microbiome analysis. For known or predicted deleterious mutations of suspected inheritance trait detected during the trial, the process would be aided by making sure that patients carrying these mutations get referred for genetic counseling and CLIA certified germline analysis. The Miami Cancer Institute has these services readily available.

The evaluation of the microbiome in stool samples will be aimed to derive clusters of patients with distinct microbiomes and given the geographic and cultural diversity of our special population in Miami to preliminary observed differences that could be attributed to environment/dietary practices associated with certain ethnicities or by time in life of immigration to the USA. Association to clinical endpoints will be documented, with no formal statistics assess, but may serve as hypothesis generating for future studies.

13.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

13.0 Investigational Product

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

All Miami Cancer Institute investigational drugs are kept in the pharmacy separate from routine drug stock and are stored according to the manufacturer and sponsor specifications. Investigational products requiring refrigeration are kept in a locked refrigerator designated for research drugs only. Room temperature investigational products also kept in the pharmacy in a secured research cabinet. Temperature monitoring is reviewed and recorded on a daily basis during normal business hours by Isensix, a real-time, wireless system that continuously monitors and records temperatures. The system also provides real time automatic alerts when sensors record data that is outside of the unit's operating range.

Table 12. Product Descriptions

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

13.1 Packaging and Labeling Information

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

13.2 Clinical Supplies Disclosure

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

13.3 Storage and Handling Requirements

Investigational products will be prepared and dispensed by a licensed pharmacist and certified pharmacy technician.

All orders will be checked by 2 pharmacy staff personnel to ensure correct preparation and labeling.

All products that are not received pre-labeled will be labeled according to federal regulations.

Accountability of investigational products will be performed and documented by pharmacy.

Investigational products will be stored and monitored in accordance with protocol-specific instructions.

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.

13.4 Returns and Reconciliation

The Miami Cancer Institute has a dedicated Investigational Drug Service (IDS), including a dedicated IDS Supervisor who leads the coordination of investigational drugs services for clinical research at Miami Cancer Institute. The IDS team provides required pharmacy services for investigational drug studies including oversight of drug storage, handling, preparation, deposition, medication dosing, staff education, and other related activities. All pharmacists involved in the compounding of investigational products are trained on each individual protocol in regards to receipt, preparation, storage, dispensing and administration, product reconciliation and source documentation. Additionally, all pharmacists involved in the compounding aspect are CITI trained and listed on the delegation of authority.

- Disposition and/or destruction of IPs following drug accountability are performed according to specific instructions provided by the sponsor and/or protocol. Disposal and/or destruction of investigational products on-site are performed in accordance with BHM BCH administrative policy

- All products will be disposed of according to regulatory requirements according to institutional policy and in accordance with the Environmental Protection Agency and the State of Florida Department of Transportation (DOT) regulations for hazardous and non-hazardous pharmaceutical waste.

- Disposition of the investigational product must be witnessed by two members of the research team and documented per institutional policy

- Documentation of IDS accountability will be performed from the time of initial product receipt through the destruction or return of the product to the supplier

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

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

14.0 ADMINISTRATIVE AND REGULATORY DETAILS

14.0.1 Confidentiality of Data

Both the investigator and the Sponsor affirm that information regarding this trial will be maintained in confidence, and such information will be divulged to the institutional review board, ethics review committee (IRB/ERC) or similar or expert committee; affiliated institution and employees, only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees. Data generated by this trial will be considered confidential by the Sponsor and the investigator.

14.0.2 Confidentiality of Subject Records

The investigator agrees that the Sponsor (or Sponsor representative), IRB/ERC, or regulatory authority representatives may consult and/or copy trial documents in order to verify worksheet/case report form data. By signing the consent form, the subject agrees to this process. If trial documents will be photocopied during the process of verifying worksheet/case

report form information, the subject will be identified by unique code only; full names/initials will be masked prior to transmission to the Sponsor.

The investigator and Sponsor agree to treat all subject data used and disclosed in connection with this trial in accordance with all applicable privacy laws, rules and regulations.

14.0.3 Confidentiality of Investigator Information

The investigator recognizes that certain personal identifying information with respect to the investigator, and all sub-investigators and trial site personnel, may be used and disclosed for trial management purposes, as part of a regulatory submission, and as required by law. This information may include:

1. Name, address, telephone number and e-mail address;
2. Hospital or clinic address and telephone number;
3. Curriculum vitae or other summary of qualifications and credentials; and
4. Other professional documentation.

Consistent with the purposes described above, this information may be transmitted to the Sponsor, and subsidiaries, affiliates and agents of the Sponsor, in your country and other countries, including countries that do not have laws protecting such information. Additionally, the investigator’s name and business contact information may be included when reporting certain serious adverse events to regulatory authorities or to other investigators. By signing this protocol, the investigator expressly consents to these uses and disclosures.

14.0.4 Confidentiality of IRB/IEC Information

The Sponsor is required to record the name and address of each IRB/IEC that reviews and approves this trial. The Sponsor is also required to document that each IRB/IEC meets regulatory and ICH GCP requirements by requesting and maintaining records of the names and qualifications of the IRB/IEC members and to make these records available for regulatory agency review upon request by those agencies.

15.0 Compliance with Financial Disclosure Requirements

Financial Disclosure requirements are outlined in the US Food and Drug Administration Regulations, Financial Disclosure by Clinical Investigators (21 CFR Part 54). It is the Sponsor's responsibility to determine, based on these regulations, whether a request for Financial Disclosure information is required. It is the investigator's/subinvestigator's responsibility to comply with any such request.

The investigator/subinvestigator(s) agree, if requested by the Sponsor in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Sponsor to allow for the submission of complete and accurate certification and disclosure statements. The

investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, commonly known as a financial disclosure form, provided by the Sponsor. The investigator/subinvestigator(s) also consent to the transmission of this information to the Sponsor in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

15.1 Compliance with Law, Audit and Debarment

The investigator agrees to conduct the trial in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of Good Clinical Practice (e.g., International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice: Consolidated Guideline and other generally accepted standards of good clinical practice); and all applicable federal, state and local laws, rules and regulations relating to the conduct of the clinical trial.

The investigator also agrees to allow monitoring, audits, IRB/ERC review and regulatory authority inspection of trial-related documents and procedures and provide for direct access to all trial-related source data and documents.

The investigator agrees not to seek reimbursement from subjects, their insurance providers or from government programs for procedures included as part of the trial reimbursed to the investigator by the Sponsor.

The investigator shall prepare and maintain complete and accurate trial documentation in compliance with Good Clinical Practice standards and applicable federal, state and local laws, rules and regulations; and, for each subject participating in the trial, provide all data, and, upon completion or termination of the clinical trial, submit any other reports to the Sponsor as required by this protocol or as otherwise required pursuant to any agreement with the Sponsor.

Trial documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the trial site upon request for inspection, copying, review and audit at reasonable times by representatives of the Sponsor or any regulatory authorities. The investigator agrees to promptly take any reasonable steps that are requested by the Sponsor as a result of an audit to cure deficiencies in the trial documentation and worksheets/case report forms.

The investigator must maintain copies of all documentation and records relating to the conduct of the trial in compliance with all applicable legal and regulatory requirements. This documentation includes, but is not limited to, the protocol, worksheets/case report forms, advertising for subject participation, adverse event reports, subject source data, correspondence with regulatory authorities and IRBs/ERCs, consent forms, investigator's curricula vitae, monitor visit logs, laboratory reference ranges, laboratory certification or quality control procedures and laboratory director curriculum vitae. The investigator agrees that documentation shall be retained until at least 2 years after the last approval of a marketing

application in an ICH region or until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product.

Because the clinical development and marketing application process is variable, it is anticipated that the retention period can be up to 15 years or longer after protocol database lock. The Sponsor will determine the minimum retention period and notify the investigator when documents may be destroyed. The Sponsor will determine the minimum retention period and upon request, will provide guidance to the investigator when documents no longer need to be retained. The sponsor also recognizes that documents may need to be retained for a longer period if required by local regulatory requirements. All trial documents shall be made available if required by relevant regulatory authorities. The investigator must consult with and obtain written approval by the Sponsor prior to destroying trial and/or subject files.

ICH Good Clinical Practice guidelines recommend that the investigator inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed.

The investigator will promptly inform the Sponsor of any regulatory authority inspection conducted for this trial.

Persons debarred from conducting or working on clinical trials by any court or regulatory authority will not be allowed to conduct or work on this Sponsor's trials. The investigator will immediately disclose in writing to the Sponsor if any person who is involved in conducting the trial is debarred or if any proceeding for debarment is pending or, to the best of the investigator's knowledge, threatened.

In the event the Sponsor prematurely terminates a particular trial site, the Sponsor will promptly notify that trial site's IRB/IEC.

16.0 Compliance with Trial Registration and Results Posting Requirements

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

The Sponsor agrees to be responsible for implementing and maintaining a quality management system with written development procedures and functional area standard operating procedures (SOPs) to ensure that trials are conducted and data are generated, documented, and reported in compliance with the protocol, accepted standards of Good Clinical Practice, and

all applicable federal, state, and local laws, rules and regulations relating to the conduct of the clinical trial.

The Quality Assurance (QA) division in the Miami Cancer Institute Clinical Trials Office is responsible for ensuring that industry standards of quality are met and exceeded on an on-going basis. The division is responsible for the identification, management, and prevention of quality issues, reviewing subject research charts, and mapping out current processes. They develop and implement quality and verification checks, including necessary assessment tools and checklists used during the QC process. Moreover, they facilitate and advice on corrections and corrective and preventive actions related to quality issues, provide guidance on interpretation and application of regulations, manage FDA and sponsor site visits, and work with site manager to create, implement, and evaluate action plans.

17.0 DATA MANAGEMENT

The Miami Cancer Institute Clinical Trials Office oversees record keeping and handling of data is to record, store, transfer and, where necessary, convert efficiently and accurately, the information gathered on each trial subject into data.

All steps involved in data management should be documented in order to allow step-by-step retrospective assessment of quality of the data and the performance of the clinical trial (the "audit paper trail" concept). Documentation is facilitated by methods such as the use of check-lists and forms giving details of action taken, dates, the individuals responsible, etc.

In the event of electronic data handling, confidentiality of the database must be secured by safety procedures such as passwords and written assurances from all staff involved. Provision must be made for the satisfactory maintenance of the database and for back-up procedures.

17.1 Responsibilities of the investigator

a) The investigator has overall responsibility for ensuring the accuracy and completeness of data entry. The investigator must ensure that the observations and findings are recorded correctly and completely in the case-report forms (CRFs) and signed by the responsible person designated in the protocol. When conducting a study and using CRFs to report clinical trial data to the sponsor, the investigator must also ensure that the routine requirements for recording of data in the source documents (e.g. hospital and laboratory records, consultation files) are met, particularly those relating to the treatment given to the subject and adverse events.

b) If trial data are entered directly into a computer, there must always be an adequate safeguard to ensure validation, including a signed and dated print-out and back-up records. Computerized systems should be validated and a detailed description for their use be produced and kept up-to-date.

c) All corrections to CRFs and to raw data must be made in a way which does not obscure the original entry. The correct data must be inserted with the reason for the correction (if not obvious), the date, and the initials of the investigator or authorized person. For electronic data processing, only authorized persons should be permitted to enter or modify data in the computer and there should be a record of changes and deletions. If data are altered during processing, the alteration must be documented.

d) Laboratory values with normal reference ranges, preferably together with the specificity and sensitivity of the methods used, should always be recorded on the CRF or be attached to it. Values outside a clinically accepted reference range or values that differ significantly from previous values must be evaluated and commented upon by the investigator.

e) Data other than those required by the protocol may appear on the CRF, provided they are clearly marked as additional or optional findings, with an explanation of their significance.

f) Units of measurement must always be stated, and conversion of units must always be indicated and documented.

g) The final report of the trial should be drawn up as defined in the protocol. The report should be signed by the sponsor, monitor and investigator(s) as well as the responsible statistician, in accordance with the applicable regulations.

h) For a period of time defined by national regulations, the investigator should maintain a confidential record to allow the translation of the unambiguous code used to conceal the identity of the individual subjects in the trial (subject identification code). The investigator may submit the subject identification code list to the drug regulatory authority after the trial, together with the final report, according to national regulations.

i) Theinvestigatorshouldensurethatthesubject'sparticipationintheclinicaltrialisclearly marked in his or her medical records.

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APPENDICES

ECOG Performance Status

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

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

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