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Title: Phase II Trial of Pembrolizumab in Recurrent or Metastatic Medullary Thyroid Cancer

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Commercial Agent: Pembrolizumab will be supplied by the manufacturer, Merck

PRÉCIS

Background:

- Anti PD1/PDL1 therapies have had clinical success in a minority of unselected patients across multiple tumor types
- While many questions remain about optimal PD1/PDL1 staining techniques to pre-select responders, less focus is being place on how to optimize responses in a broader cohort of patients
- Emerging preclinical and clinical data supports the hypothesis that a strong immunologic response in the tumor microenvironment induces PDL1 expression on the tumor and is associated with better clinical response to anti-PD1/PDL1 therapies
- Therapeutic cancer vaccines are one strategy to induce an immunologic response to the tumor, thereby enhancing PDL1 expression and optimizing clinical responses across all patients
- Limited clinical data exists about the potential benefit of sequential therapy with a therapeutic cancer vaccine followed by PD1/PDL1 inhibition
- This study will explore the role of PD1 inhibition in medullary thyroid cancer and evaluate the potential differences based on previous vaccine therapy

Objective:

- The primary objective of this trial is to determine whether administering a PD1 inhibitor to patients with medullary thyroid cancer will permit a modest fraction to be able to experience a 50% or greater decline in calcitonin levels or experience a partial/complete response on imaging

Key Eligibility:

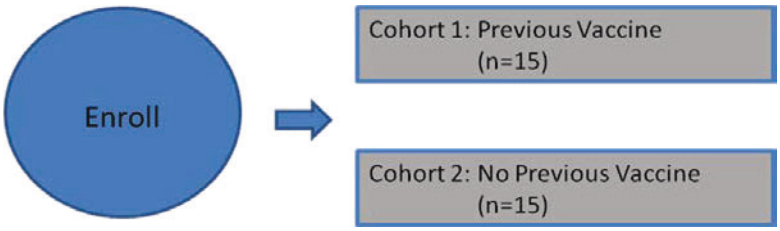
- Patients ≥ 18 years of age with evidence of metastatic medullary thyroid cancer including disease that is evaluable on bone, CT scan or MRI
- Must have elevated calcitonin levels greater than 40 pg/mL
- Patients with minimal or no disease related-symptoms (minimal symptoms will include those that do not affect activities of daily living or pain that does not require regularly schedule narcotics)
- ECOG 0-1
- Should have no autoimmune diseases; no evidence of being immunocompromised; no serious inter-current medical illness
- No brain metastasis, history of seizures, encephalitis, or multiple sclerosis

Design:

- This is a phase II, open label, single center clinical trial where all patients receive the anti-PD1/PDL1 therapy pembrolizumab

- Patients will enroll in one of two cohorts: patients with previous vaccine therapy or patients without previous vaccine therapy
- All patients will be TKI -naïve, with minimal symptoms (consistent with the eligibility for our current study)
- Based on our calcitonin findings with our current study of 30 patients, we have determined that a confirmed calcitonin decline of 50% would be a rare finding, providing compelling preliminary evidence of clinical activity
- A total of 30 patients will be enrolled in the proposed study (15 patients in each cohort). Given that we already have 30 patients on a study with vaccine, we would only need to identify and recruit 15 naïve patients for the vaccine-naïve cohort. This accrual could be done in 18 months based on our current accrual rates
- Based on these metrics, we could have >6 months of calcitonin data in 30 patients within 2 years from trial initiation
- Additional immune correlative capitalizing on the extensive immune monitoring experience of the LTIB will allow for assessments of antigen specific T-cells and 123 immune subsets. These findings could provide the basis for biomarker development when taken together with biochemical and clinical responses seen in this study

SCHEMA



Treatment Duration with Pembrolizumab: 2 years (at 3 week intervals)

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1.1 Study Objectives

1.1.1 Primary Objectives

- Determine whether administering a PD1 inhibitor to patients with medullary thyroid cancer will permit a modest fraction to be able to experience a 50% or greater decline in calcitonin levels or experience partial/complete response on imaging. Based on our calcitonin findings with our current study of 30 patients, we have determined that a confirmed calcitonin decline of 50% would be a rare finding, providing compelling preliminary evidence of clinical activity.

1.1.2 Secondary Objectives

- Determine the impact of previous therapeutic cancer vaccine on response rates
- Evaluate immune responses in each cohort
- Evaluate changes in CEA and Calcitonin kinetics
- Evaluate impact on progression free survival and overall survival
- Evaluate the safety of anti-PD1/PDL1 therapy pembrolizumab

1.2 Background and Rationale

Background

Therapies targeting the PDL1/PD1 axis have become the primary focus of clinical immunotherapy development as a substantial amount of academic and industry resources are being used to develop these therapies. Several diseases have been noted for their impressive responses in individual patients (bladder cancer, lung cancer and melanoma) and emerging data suggest benefit across a broad range of tumors. Despite these impressive findings, regardless of tumor type, only a minority of patients have response to this therapy.[1] A lot of effort is being expended to develop a biomarker predicting response (such as PDL1 expression by the tumor) but techniques and standards remain elusive. A key focus of this study is to determine if therapeutic cancer vaccines can enhance responses to pembrolizumab, providing a proof of concept that sequential therapy with vaccine followed by checkpoint inhibition can optimize clinical and immunologic responses. If this hypothesis is correct, this study could define a technique substantially enhance the proportion of patients who respond the immune checkpoint inhibition with agents such as pembrolizumab.

Medullary Thyroid Cancer

Medullary thyroid cancer (MTC) is a neuroendocrine tumor of the parafollicular or C cells of the thyroid gland. MTC accounts for approximately 4% of thyroid carcinomas. Its estimated incidence in the United States for 2010 is about 1,300 to 2,200 patients. Sporadic MTC accounts for about 80% of all cases of the disease. The typical age of presentation is in the fifth

or sixth decade, and there may be a slight female preponderance.[2] Surgery is the only curative treatment for MTC and consists of total thyroidectomy with bilateral central lymphadenectomy. [3]

When there is no anatomic evidence of disease, despite detectable serum calcitonin or CEA, the best current option is observation.[4] Therapeutic interventions at this stage of disease have not demonstrated clinical benefit. Empiric surgical procedures aimed to remove all the lymph nodes of the neck and the mediastinum have been proposed, but the results have largely been disappointing. These procedures may yield no tumor resection and are unlikely to provide a biochemical remission. Patients with rapidly progressive disease by anatomic imaging or biochemical doubling time < 2 years should be considered for treatment, ideally in the context of a well-designed clinical trial.[5]

Metastatic MTC is largely unresponsive to conventional cytotoxic chemotherapy and radiotherapy.[6] Until recently, doxorubicin was the only US Food and Drug Administration (FDA)–approved treatment for patients with advanced thyroid cancer. Doxorubicin has resulted in transient tumor response rates in up to 20% of patients with MTC and is associated with significant toxicity.[7]

Promising results have been reported with vandetanib, an oral inhibitor of VEGFR, RET, and epidermal growth factor receptor (EGFR).[8,9] An international randomized phase III trial of vandetanib (300 mg daily) was performed in patients with either sporadic or hereditary MTC. In a preliminary report of results (median follow-up 24 months), median progression-free survival was improved in patients randomly assigned to vandetanib versus placebo (hazard ratio 0.45, 95% CI 0.30 to 0.69). [10] Based on these results, vandetanib was approved by the FDA in April 2011 for patients with late-stage (metastatic) MTC who are ineligible for surgery and who have disease that is growing or causing symptoms.[11] Its toxicity profile is extensive including diarrhea (56%), rash (45%) nausea (33%), hypertension (32%) headache (26%), fatigue (24%), decreased appetite (21%); Grade 3 toxicities include diarrhea (11%), hypertension (9%) and fatigue (6%). Therefore, toxicity limits its use in patients with small volume, asymptomatic or indolent disease.

Similarly cabozantinib has demonstrated improvement in PFS in a population of patients with advanced MTC (estimated median PFS was 11.2 months for cabozantinib versus 4.0 months for placebo (hazard ratio, 0.28; 95% CI, 0.19 to 0.40; P < .001) and is now FDA approved in MTC.[12] Unfortunately, toxicity was also significant with this treatment with common associated adverse events including diarrhea, palmar-plantar erythrodysesthesia, decreased weight and appetite, nausea, and fatigue. The impact of toxicity on the patients was clearly indicated based on the fact that 70% of patients required dose reductions and dosing delays in 65% of patients.

Given the toxicity with these FDA approved agents, patients and practitioners alike often delay treatment until patients have symptoms commensurate with the toxicity profile or a rapid pace of disease. As demonstrated by the accrual in our current trial (30 patients in about 2.5 years) which enrolls patients who are naïve to these TKIs, accruing to this population is feasible, representing a therapeutic window of opportunity for the proposed study.

Vaccine Therapy with GI-6207

A phase I study using the heat-killed yeast-CEA vaccine has completed accrual at the NCI. [13] A total of 25 patients enrolled in a classic phase I design at 3 dose levels: 4, 16, and 40

yeast units (divided in 4 injection sites/ each unit =10^7 yeast particles). GI-6207 was administered in equal doses at 4 sites subcutaneously in bilateral inguinal and anterior chest wall regions. GI-6207 was administered at 2-week intervals for 3 months, then monthly. Most patients were heavily pre-treated with advanced disease, a situation in which GI-6207 induced immune response can be difficult to generate.

Of 25 evaluable patients, 5 patients (3 colon cancer, 1 MTC and 1 non-small cell lung cancer) had stable disease beyond 3 months (18, 10, 8, 5, 4 months, respectively). All 5 pts had relative stabilization or declines in serum CEA after treatment.

Toxicity

GI-6207 was well tolerated and the most common adverse event (AE) was grade 1 or 2 injection site reaction. The complete list of toxicity (all grades) is listed in **Table 1**. One patient with MTC, who had a large pericardial (5 cm) and pleural based (over 3 cm) mass, developed pleural and pericardial effusions (with associated pneumonitis, dyspnea) that may have been associated with a robust anti-tumor immune response. (These symptoms resolved within 48 hour after steroids were administered). Another patient with NSCLC developed recurrent pleural effusion which responded to oral steroids. The grade 3 back and abdominal pain were observed in a patient with rapidly progressing colon cancer with pre-existing ascites which was more likely the cause of these two events.

Table 1: **Phase I CEA yeast toxicities (all grade toxicities with attribution 3 or higher)**

	GRADE 1		GRADE 2		GRADE 3	
AE	# pts	# events	# pts	# events	# pts	# events
Abdominal Pain	0	0	0	0	1	1
Anemia	1	1	0	0	0	0
Back pain	0	0	0	0	1	1
Bruising	1	1	0	0	0	0
Chest Wall Pain	1	1	0	0	0	0
Chills	1	1	0	0	0	0
Dyspnea	0	0	0	0	1	1
Edema	1	1	0	0	0	0
Elevated AST	0	0	1	1	0	0
Fatigue	5	5	0	0	0	0
Fever	1	1	1	1	1	1
Flu-like syndrome	3	3	1	1	0	0
Flushing	1	1	0	0	0	0
Headache	1	1	1	1	0	0
Hypoxia	0	0	0	0	1	1
Injection site reaction	12	34	1	6	0	0

	GRADE 1		GRADE 2		GRADE 3	
AE	# pts	# events	# pts	# events	# pts	# events
Myalgia	2	2	1	1	0	0
Nausea	1	1	0	0	0	0
Pain	1	1	0	0	1	1
Thrombocytopenia	1	1	0	0	0	0
Pleural Effusion	0	0	1	1	1	1
Proteinuria	1	1	0	0	0	0
Pruritis	1	1	0	0	0	0
Rash	0	0	1	1	0	0
Pneumonitis	0	0	0	0	1	1

Immune Responses with GI-6207

Although this was a heavily pre-treated population of patients with advanced disease, there were some immunologic parameters that suggested GI-6207 induced an immune response. Interferon-gamma ELISPOT assays (CEA and MUC1) were performed in 9 HLA2 and HLA3 positive patients pre - vs. post- vaccination. Antigen-specific T-cell responses were detected (a minimum of a 2-fold increase from baseline) in 5 out of 9 patients. One of these patients was the MTC who had a greater than 20-fold increases in antigen-specific T-cell responses compared to baseline. The number and phenotype of NK cells was determined by analysis using CD56, CD3, and CD16 in 13 patients. NK cells may represent increased innate activity of the immune system after GI-6207. Six of 13 evaluable patients had increased, 5 had unchanged and 2 had decreased NK frequency. 3 out of 4 evaluable patients with stable had increased NK frequency (including patient with MTC).

Treg levels were determined by 7-color flow cytometry analysis using CD4, CD25, CD127, FoxP3, CTLA-4, CD45RA, and CD8. Effector/Treg ratios (pre - vs. post GI-6207 administration) were calculated in 16 evaluable patients. Eight of 16 evaluable patients had increased Effector/Treg ratio, suggesting that T-cells were more active after treatment. MDSC (myeloid-derived suppressor cell) frequency (monocytic and granulocytic) were determined in 13 patients by flow cytometry analysis using CD14, CD11b, CD15, CD33, CD13, and DR. Five of 13 evaluable pts had decreased MDSC levels, 6 had unchanged and 2 had increased MDSC levels. These data suggest GI-6207 did not increase immune suppressive activity within treated patients, and some patients had relative increases in effector T-cells after treatment.

Inflammatory Reactions Seen after Treatment with GI-6207

Phase I Data Suggest GI-6207 has immunologic activity as described above. In addition, 2 patients have had substantial inflammatory responses. One is pictured below. [13] A second

patient in the current MTC trial has had a similar episode followed by fluctuating, but now declining calcitonin.

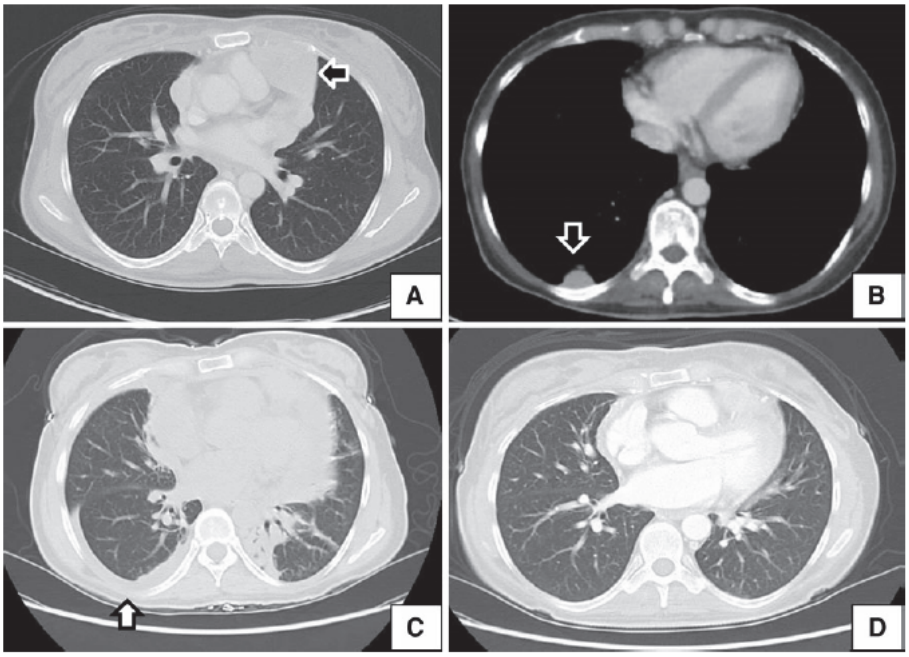


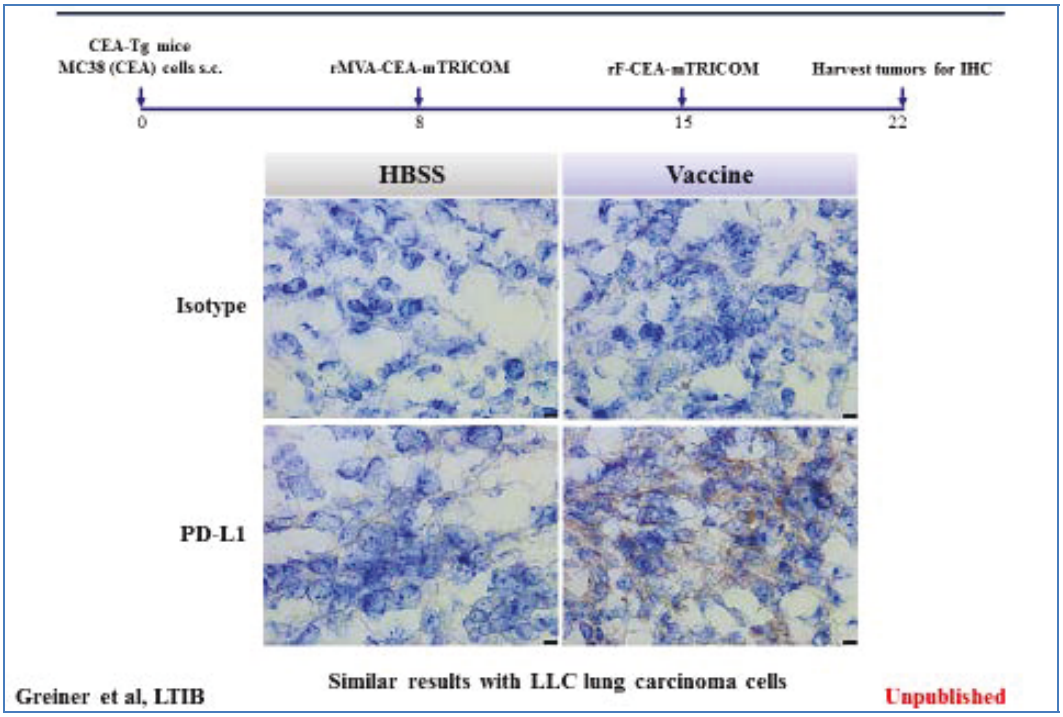
Figure 1. Inflammatory response in a patient with medullary thyroid cancer who was treated with vaccine. Frames A and B: Baseline computed tomography (CT) of a patient with medullary thyroid cancer who had a pericardial-based lesion (a, arrow) and a right-sided pleural-based lesion (b, arrow). Frame C: Six days after the seventh vaccine (approximately 13 weeks after initiating therapy), the patient developed shortness of breath and was admitted to a local hospital. CT showed a right-sided pleural effusion and a pericardial effusion. A biopsy evaluating lymphangitic spread, bronchoscopy with lavage, and empiric antibiotic therapy yielded no clear etiology. With no clear diagnosis, high-dose steroids were started to treat a potential immune-related reaction. The patient's symptoms resolved within 48 h. Frame D: CT image obtained 18 days after the image in (C) and approximately 2 weeks after starting steroids. Notably, this patient was re-evaluated for yeast allergies and found to be negative, and the magnitude of antigen-specific T cell response to multiple tumor antigens increased 10- to 20-fold after vaccine. Based on the clinical course and absence of an alternative diagnosis, it is possible that this was a vigorous immune-mediated antitumor response. Interestingly, in image (C), the effusion was only on the right side (arrow), the same location of the pleural-based lesion seen in (B) [13]

Rationale for Using Vaccines to Enhance Responses to PD1/PDL1 blockade

Unlike targets of other precision therapies, PDL1 expression is not a somatic mutation that is inherent to the cancer itself. PDL1 expression is dynamic and likely a reaction of the cancer cells to immune cells in the tumor microenvironment. One can think of it as a "footprint" suggesting an activated T-cell response was or is there [14]. Thus PDL1/PD1 inhibitors are essentially enabling neutralized immune cells already in the tumor microenvironment to bypass

the tissue preserving inhibitory T-cell signaling through PD1/PDL1 and kill cancer cells. There is actually substantial evidence from colon cancer, that the presence of immune cells in resected samples is strongly associated with clinical outcomes, demonstrating the potential clinical impact of immune activity against cancer cells. [15] Similar data is also emerging across many other tumor types. [16] Taken a step further, cancer cells that can neutralize immune cells, perhaps with immune checkpoint inhibitors such as PDL1 have a greater likelihood of clonal propagation within a patient.

Figure 2: Effect of Vaccination on Tumor PD-L1 Expression

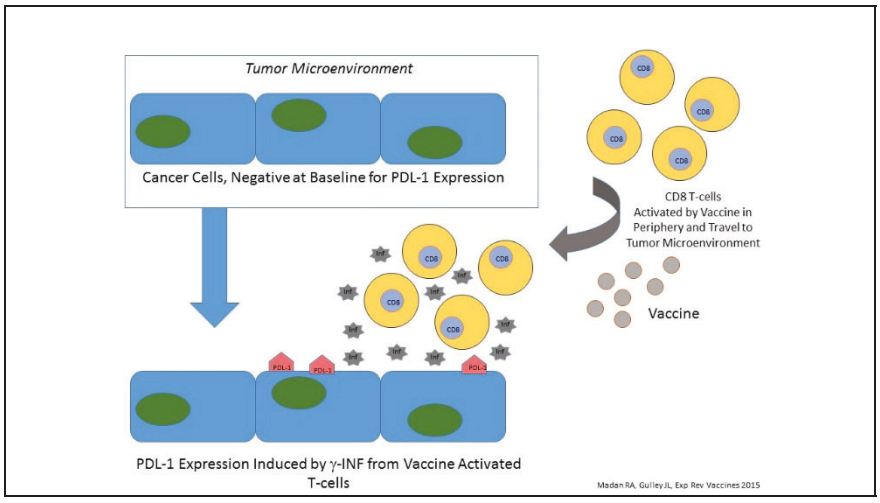


One study done in the LTIB (unpublished, Greiner Lab) demonstrates that vaccine can indeed enhance tumor expression by tumor cells. These studies included a CEA-targeting vaccine and two cell line, MC38 (pictured) and Lewis Lung cancer

There is also growing data suggesting the mechanism by which immune cells in the tumor microenvironment may lead to increased PDL1 expression on tumor cells. Multiple studies have implicated INF-γ as one mediator PDL1 expression by tumor cells. INF-γ is a cytokine produced by activated T-cells, and thus biologically it would seem that it is a rational mechanistic trigger for PDL1 expression. Preclinical and clinical data supports this hypothesis.[17,18] Preclinical studies evaluating established B16 tumors in C57BL/6, Balb/c mice demonstrated that vaccine combined with anti-PDL1 therapy had the greatest impact on tumor growth compared to vaccine or controls alone. Interestingly, that benefit was negated when an antibody binding to INF-γ was introduce into the model, demonstrating its important role in the synergy of the two therapies. Also, interesting findings were noted when human tumors were evaluated for INF-γ. Tissue in melanoma patients that had increased genetic expression of genes consistent with INF-γ production were associated with the greatest responses to anti-PD1 therapy.

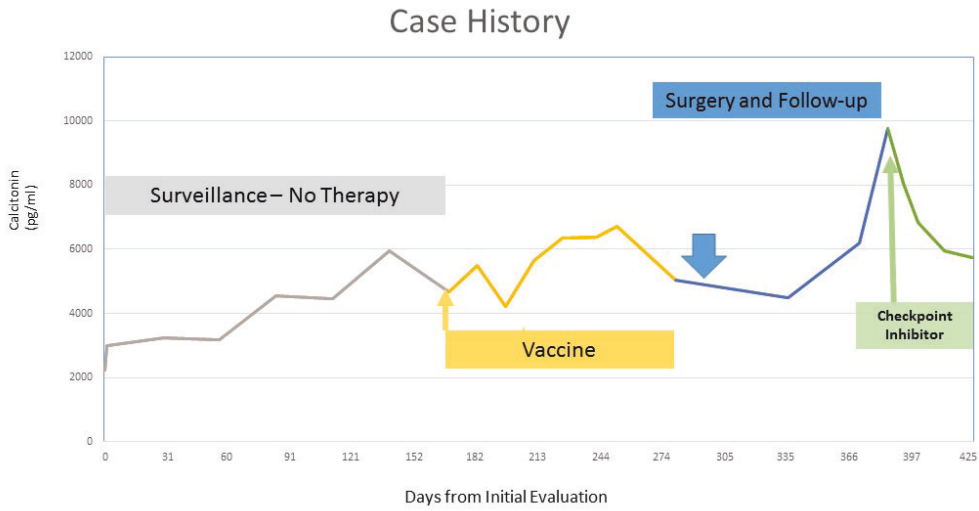
Based on this perspective, combining or sequencing vaccines with anti-PDL1/PD1 therapies could broaden the clinical benefit to include a greater proportion of patients that are currently unable to benefit from immune checkpoint inhibition. Increasing peripheral T-cell activation with vaccines, thereby enabling these cells to then migrate to the tumor microenvironment may be one strategy to improve response rates to anti-PDL1/PD1 therapies.

Figure 3. Vaccines may prime the tumor microenvironment to increase response rate to anti-PD1 inhibitors.



Case Report: Patient who received Vaccine and then a PD1/PDL1 Checkpoint Inhibitor

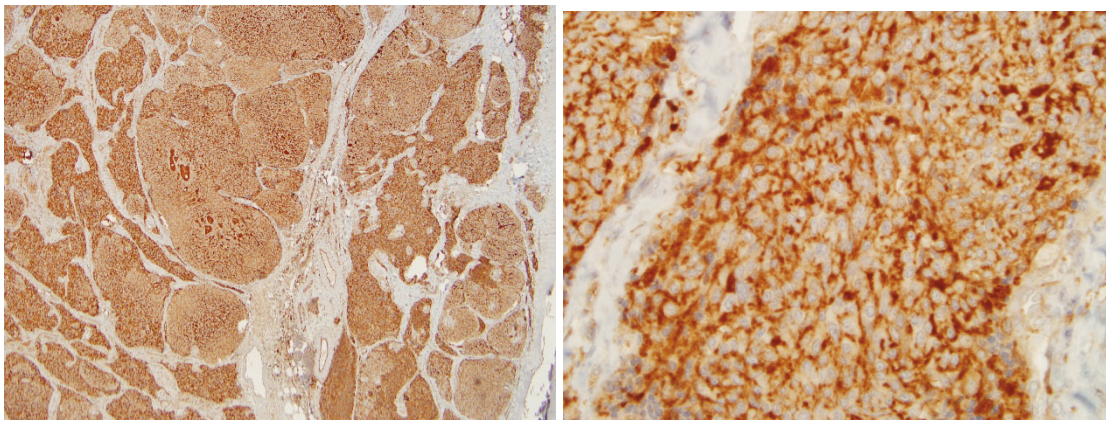
Figure 4



This case report in **Figure 4** is (unpublished) data from a male with MTC who was surveilled for 6 months prior to getting 4 months of vaccine. During surveillance he had doubling time (one method to measure tumor growth rate) of approximately 135 days. During the vaccine period his doubling time improved/was prolonged to approximately 530 days. He then came off vaccine for elective surgery and per protocol had to discontinue vaccine. When seen in follow up, his calcitonin was rising again after surgery. At that point, approximately 3 months after surgery, he enrolled on a PDL1 inhibitor with a calcitonin of 9765 pg/ml. (Calcitonin stabilization after surgery may vary based on disease burden, but within 1 month it would be expected to achieve maximum decline. [19] He then had 5 consecutive declines in his calcitonin to 5732 pg/ml while on the immune checkpoint inhibitor, a greater than 40% decline. At this time, he had an immune related adverse event (asymptomatic rise in lab values) that required discontinuation of therapy. With extensive toxicity data from pembrolizumab, in the proposed phase II trial PD1/PDL1 inhibition would not be discontinued for asymptomatic lab values such as the case in this patient who was on a phase I trial which has stricter guidelines.

Although this patient's peripheral immune response has not been evaluated yet, his lymph node with tumor resected at surgery was evaluated for PDL1 expression. The staining of this sample was robustly positive for PDL1 expression. (No baseline sample was available for evaluation given that patient was diagnosed over 15 years ago.)

Figure 5. Robustly positive PDL1 staining after surgical resection of a neck lymph node after vaccine (higher power on the right.)



These data suggest that a patient with a rapidly rising calcitonin, had his calcitonin doubling time slowed (improved) while on vaccine. The vaccine was discontinued per protocol as the patient elected to have surgical resection, but after a transient decline in calcitonin, his values began to rise again. At this point he enrolled on a clinical trial of an immune checkpoint inhibitor targeting the PD1/PDL1 axis and had a rapid, substantial (>40%) decline in his calcitonin. While on the phase I trial of the checkpoint inhibitor, the patient had asymptomatic changes in lab values, which led to protocol mandated treatment discontinuation. This decline in terms of percentage and consecutive values demonstrating a confirmed decline has not been seen in any of the 30 patients with MTC who were are currently following for up to 30 months. Evaluation of resected tumor indicates strong PDL1 expression.

Pembrolizumab

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

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an Ig superfamily member related to CD28 and CTLA-4 which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2). The structure of murine PD-1 has been resolved. PD-1 and family members are type I transmembrane glycoproteins containing an Ig Variable-type (V-type) domain responsible for ligand binding and a cytoplasmic tail which is responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM). Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3ζ, PKCθ and ZAP70

which are involved in the CD3 T-cell signaling cascade. The mechanism by which PD-1 down modulates T-cell responses is similar to, but distinct from that of CTLA-4 as both molecules regulate an overlapping set of signaling proteins. PD-1 was shown to be expressed on activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B-cells, T regs and Natural Killer cells. Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells. The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types, including non-hematopoietic tissues as well as in various tumors. Both ligands are type I transmembrane receptors containing both IgV- and IgC-like domains in the extracellular region and contain short cytoplasmic regions with no known signaling motifs. Binding of either PD-1 ligand to PD-1 inhibits T-cell activation triggered through the T-cell receptor. PD-L1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments. PD-L2 is thought to control immune T-cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T-cell function in peripheral tissues. Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor. PD-1 has been suggested to regulate tumor-specific T-cell expansion in subjects with melanoma (MEL). This suggests that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and should be considered as an attractive target for therapeutic intervention.

Pembrolizumab is a potent and highly selective humanized monoclonal antibody (mAb) of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Pembrolizumab™ (pembrolizumab) has recently been approved in the United Stated for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilumumab and, if BRAF V600 mutation positive, a BRAF inhibitor.

1.2.1 Rationale for Dose Selection/Regimen/Modification

An open-label Phase I trial (Protocol 001) is being conducted to evaluate the safety and clinical activity of single agent pembrolizumab (MK-3475). The dose escalation portion of this trial evaluated three dose levels, 1 mg/kg, 3 mg/kg, and 10 mg/kg, administered every 2 weeks (Q2W) in subjects with advanced solid tumors. All three dose levels were well tolerated and no dose-limiting toxicities were observed. This first in human study of pembrolizumab (MK-3475) showed evidence of target engagement and objective evidence of tumor size reduction at all dose levels (1 mg/kg, 3 mg/kg and 10 mg/kg Q2W). No MTD has been identified to date. 10.0 mg/kg Q2W, the highest dose tested in PN001, will be the dose and schedule utilized in Cohorts A, B, C and D of this protocol to test for initial tumor activity. Recent data from other clinical studies within the pembrolizumab (MK-3475) program has shown that a lower dose of pembrolizumab (MK-3475) and a less frequent schedule may be sufficient for target engagement and clinical activity.

PK data analysis of pembrolizumab (MK-3475) administered Q2W and Q3W showed slow systemic clearance, limited volume of distribution, and a long half-life (refer to IB).

Pharmacodynamic data (IL-2 release assay) suggested that peripheral target engagement is durable (>21 days). This early PK and pharmacodynamic data provides scientific rationale for testing a Q2W and Q3W dosing schedule.

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

The rationale for further exploration of 2 mg/kg and comparable doses of pembrolizumab in solid tumors is based on: 1) similar efficacy and safety of pembrolizumab when dosed at either 2 mg/kg or 10 mg/kg Q3W in melanoma patients[20] 2) the flat exposure-response relationships of pembrolizumab for both efficacy and safety in the dose ranges of 2 mg/kg Q3W to 10 mg/kg Q3W, 3) the lack of effect of tumor burden or indication on distribution behavior of pembrolizumab (as assessed by the population PK model) and 4) the assumption that the dynamics of pembrolizumab target engagement will not vary meaningfully with tumor type.

The choice 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.

2 ELIGIBILITY ASSESSMENT AND ENROLLMENT

2.1 Eligibility Criteria

2.1.1 Inclusion Criteria

2.1.1.1 Diagnosis: Patients must have histologically confirmed medullary thyroid cancer by the Laboratory of Pathology or a pathology report and history consistent with medullary thyroid cancer. It is not uncommon for a secondary, minor pathologic focus of another form of thyroid cancer to be coincidentally found in 15-20% of patients with medullary thyroid cancer[21]. In such cases, eligibility is based on the discretion of the investigator.

2.1.1.2 Patients must have evidence of metastatic medullary thyroid cancer including disease that is evaluable on bone, CT scan or MRI. (Patients who are surgical candidates and potentially rendered disease free with surgical resection are not eligible.)

2.1.1.3 Patients must have elevated calcitonin levels greater than 40 pg/mL

2.1.1.4 Patients must have minimal or no disease related-symptoms (Minimal symptoms will include those that do not affect activities of daily living or pain that does not require regularly scheduled narcotics.)

2.1.1.5 Patients must have evaluable disease on imaging

2.1.1.6 No history of seizures, encephalitis, or multiple sclerosis.

2.1.1.7 Age ≥ 18 years

2.1.1.8 ECOG performance status of 0-1 at study entry (Karnofsky ≥ 70) (See **Appendix A**).

2.1.1.9 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.

2.1.1.10 Female subjects of childbearing potential must be willing to use an adequate method of contraception as outlined in Section **10.6**, Contraception, for the course of the study through 120 days after the last dose of study medication.

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

2.1.1.11 Male subjects of childbearing potential must agree to use an adequate method of contraception as outlined in Section **10.6**, Contraception, starting with the first dose of study therapy through 120 days after the last dose of study therapy.

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

2.1.1.12 Willing to travel to the NIH for follow-up visits

2.1.1.13 Able to understand and sign informed consent.

2.1.1.14 Demonstrate adequate organ function as defined in **Table 2**, all screening labs should be performed within 10 days of treatment initiation.

Table 2 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1,000 /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)	≤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
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
[a]Creatinine clearance should be calculated per Cockcroft-Gault equation.	

2.1.2 Exclusion Criteria

2.1.2.1 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.

2.1.2.2 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.

2.1.2.3 Has a known history of active TB (Bacillus Tuberculosis)

2.1.2.4 Hypersensitivity to pembrolizumab or any of its excipients.

2.1.2.5 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.

2.1.2.6 Has had prior 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.

2.1.2.7 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.

2.1.2.8 Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are stable for 6 months (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.

2.1.2.9 Has history of (non-infectious) pneumonitis that required steroids, evidence of interstitial lung disease or active, non-infectious pneumonitis..

2.1.2.10 Has an active infection requiring systemic therapy.

2.1.2.11 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.

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

2.1.2.13 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.

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

2.1.2.15 Has Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).

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

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

2.1.2.18 Concurrent use of systemic steroids, except for physiologic doses of systemic steroid replacement or local (topical, nasal, eye drops or inhaled) steroid use. Limited doses of systemic steroids (e.g., in patients with exacerbations of reactive airway disease or to prevent IV contrast allergic reaction or anaphylaxis in patients who have known contrast allergies) are allowed.

2.1.2.19 Serious inter-current medical illness which would interfere with the ability of the patient to carry out the treatment program.

2.1.2.20 Patients with second malignancy within 3 years of enrollment; Patients curatively treated non-melanoma skin cancers or carcinoma in situ of the bladder, are not excluded. Patients with MEN2 and a history of pheochromocytoma will also not be excluded. In addition patients with prostate cancer who do not require systemic therapy will not be excluded. (A secondary, minor pathologic focus of another form of thyroid cancer may be coincidentally found in 15-20% of patients with medullary thyroid cancer. In such cases, eligibility is based on the discretion of the investigator.)

2.1.2.21 Patients with previous history of vandetanib or cabozantinib treatment for more than 28 days of treatment (patients have discontinued treatment for 28 days before enrolling).

2.1.3 Recruitment Strategies

We have established national referral patterns from our previous study with a yeast CEA vaccine – 13-C-0095. Furthermore, many patients from the study who are still being seen at the NCI will return and enroll on this trial.

2.2 Registration Procedures

Registration will be a two-part process as patients are screened on this protocol. Authorized staff must register an eligible candidate with NCI Central Registration Office (CRO) within 24 hours of signing consent. To initially register a subject after the participant has signed the consent, complete the top portion of the registration Eligibility Checklist from the website (http://home.ccr.cancer.gov/intra/eligibility/welcome.htm) indicating that the patient is being registered for screening and send via encrypted email to: NCI Central Registration Office ncicentralregistration-l@mail.nih.gov. Once eligibility is confirmed after completion of screening studies, complete the remainder of the form which is the eligibility checklist, indicating that the patient is being registered for treatment and email the completed registration checklist to the CRO at NCI Central Registration Office ncicentralregistration-l@mail.nih.gov. After confirmation of eligibility at Central Registration Office, CRO staff will call pharmacy to advise them of the acceptance of the patient on the protocol prior to the release of any investigational agents. Verification of Registration will be forwarded electronically via e-mail to the research team. A recorder is available during non-working hours.

Subjects that do not meet screening criteria should be removed from the study following the procedure in section **3.5.3**.

2.3 Screening Evaluation

2.3.1 The following tests may be obtained any time prior to initiation of study therapy:

- Pathological confirmation of diagnosis in the Laboratory of Pathology at the NIH Clinical Center prior to starting this study when possible. Pathology reports from other hospitals and a history consistent with medullary thyroid cancer will also be sufficient for documentation of pathological confirmation.

2.3.2 The following parameters will be obtained within 8 weeks prior to initiation of study therapy:

- HIV (anti HIV 1,2 antibody)
- Hepatitis B (HBcAb IgM) and C (HCV antibody test)
- Tc-99 whole body scintigraphy (bone scan)
- CT of neck/chest/abdomen/pelvis (MRI may be substituted at investigator discretion)
- Electrocardiogram (EKG)

2.3.3 The following parameters will be obtained within 10 days prior to initiation of study therapy:

2.3.3.1 Clinical Evaluation

- History and physical examination including vital signs (blood pressure, pulse, respiratory rate, oxygen saturation
- ECOG performance status (see **Appendix A**)

2.3.3.2 Laboratory studies

- Complete blood count plus differential and platelet count
- Chemistries (sodium, potassium, chloride, CO2, creatinine, glucose, BUN, albumin, calcium, magnesium, phosphorus, alk phos, ALT, AST, total bilirubin, direct bilirubin, LD, total protein, total CK and uric acid)
- PT, PTT
- Urinalysis (may be omitted if patient is incontinent and cannot provide a urine sample)
- Serum calcitonin and CEA
- TSH
- Urine Beta-HCG for women of child-bearing age (repeated within 48 hours prior to treatment). (Serum Beta-HCG may be done if urine is positive or inconclusive).

Females of childbearing potential (FCBP): A female of childbearing potential is a sexually mature woman who:

a) Has not undergone a hysterectomy or bilateral oophorectomy

b) Has not been naturally postmenopausal for at least 24 consecutive months (i.e. has had menses at any time in the preceding 24 consecutive months).

c) Has a congenital or acquired condition that prevents childbearing

In addition, patients, both male and female, should be willing to practice effective birth control during the study and for four months following the last study treatment, unless they have had a prior hysterectomy, bilateral oophorectomy, congenital conditions associated with infertility or azoospermia.

2.4 Treatment Assignment and Randomization/Stratification Procedures:

Cohorts

Number	Name	Description
1	*First cohort*	*Patients with prior vaccine therapy*
2	*Second cohort*	*Patients without prior vaccine therapy*

Arms

Number	Name	Description
1	*Pembrolizumab*	*Pembrolizumab treatment for 2 years at Q3W*

Randomization and Arm Assignment

Patients will be enrolled to Cohort 1 (previous vaccine) or Cohort 2 (no previous vaccine) based on their treatment history. This will be established at each patients' screening visit and noted on the eligibility criteria. Patients in cohort 1 and cohort 2 will be directly assigned to Arm 1.

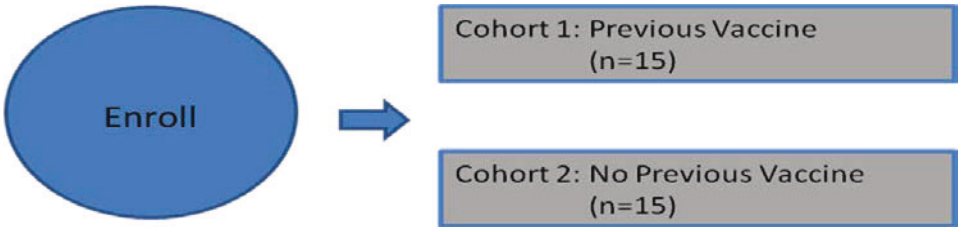
2.5 Baseline Evaluation

Screening evaluations performed within 8 weeks prior and within 10 days prior to treatment initiation will be used as baseline.

3 STUDY IMPLEMENTATION

3.1 Study Design

This will be an open label study in which all patients receive pembrolizumab. Patients will be assigned to specific cohorts based on their previous treatment with an immune stimulating therapeutic cancer vaccine.



Treatment Duration with Pembrolizumab: 2 years (at 3 week intervals)

3.2 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
Treatment Duration with Pembrolizumab: 2 years (3 week intervals)					

Trial treatment should begin on the day of enrollment or as close as possible to that date.

3.3 Drug Administration

Trial treatment should be administered on Day 1 of each cycle after all procedures/assessments have been completed as detailed on the Study Calendar (Section **3.4**). Trial treatment may be administered up to 7 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. Every effort should be made to target infusion timing to be as close to 30 minutes as possible.

However, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min). Premedication for patients who experience an infusion reaction should be administered 60 minutes (+/- 30 minutes) prior to the infusion.

The Pharmacy Manual contains specific instructions for the preparation of the pembrolizumab infusion fluid and administration of infusion solution. Pembrolizumab is administered through a 0.2 to 5 micron sterile, nonpyrogenic, low-protein binding inline or add-on filter. Do not infuse other mediations through the same infusion line.

3.3.1 Dose Modifications

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 **4** for supportive care guidelines, including use of corticosteroids.

Table 4. Dose Modification Guidelines for Drug-Related Adverse Events

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Treatment Discontinuation
Diarrhea/Colitis	2-3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	4	Permanently discontinue	Permanently discontinue
AST, ALT, or Increased Bilirubin	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose
	3-4	Permanently discontinue (see exception below)[a]	Permanently discontinue
Type 1 diabetes mellitus (if new onset) or Hyperglycemia	T1DM or 3-4	Hold pembrolizumab for new onset Type 1 diabetes mellitus or Grade 3-4 hyperglycemia associated with evidence of beta cell failure	Resume pembrolizumab when patients are clinically and metabolically stable
Hypophysitis	2-4	Toxicity resolves to Grade 0-1. Therapy with pembrolizumab can be continued while endocrine replacement therapy is instituted	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Treatment Discontinuation
Hyperthyroidism	3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	4	Permanently discontinue	Permanently discontinue
Hypothyroidism		Therapy with pembrolizumab can be continued while thyroid replacement therapy is instituted	Therapy with pembrolizumab can be continued while thyroid replacement therapy is instituted
Infusion Reaction	2[b]	Toxicity resolves to Grade 0-1	Permanently discontinue if toxicity develops despite adequate premedication
	3-4	Permanently discontinue	Permanently discontinue
Pneumonitis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	3-4	Permanently discontinue	Permanently discontinue
Renal Failure or Nephritis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	3-4	Permanently discontinue	Permanently discontinue
All Other Drug-Related Toxicity[c]	3 or Severe	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	4	Permanently discontinue	Permanently discontinue

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

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

[b] If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose; Refer to **Table 5** – Infusion Reaction Treatment Guidelines for further management details.

[c] Patients with intolerable or persistent Grade 2 drug-related AE may hold study medication at physician discretion. Permanently discontinue study drug for persistent Grade 2 adverse reactions for which treatment with study drug has been held, that do not recover to Grade 0-1 within 12 weeks of the last dose.

Dosing interruptions are permitted in the case of medical / surgical events or logistical reasons not related to study therapy (e.g., elective surgery, unrelated medical events, patient vacation, and/or holidays). Subjects should be placed back on study therapy within 6 weeks of the

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

3.3.2 Dosing Delay

Dosing delay is permitted by 7 days before or after scheduled treatment for logistical purposes (given travel requirements of our patients). If there are changes in the schedule, the subsequent dose may not be given less than 18 days later.

3.4 Study Calendar

Procedure	Screening/ Baseline[5]	Treatment Cycles (21 days +/- 7 days)[1]								Cycle 9 and beyond	Post Treatment[6]
		C1 D1	C2 D1	C3 D1	C4 D1	C5 D1	C6 D1	C7 D1	C8 D1		
History and PE	X[2]	X	X	X	X	X	X	X	X	X	X
Vital signs	X[2]	X	X	X	X	X	X	X	X	X	X
Performance Score	X[2]										
Height/Weight	X[3]										
HIV, Hep B, C	X										
Pregnancy Test (Urine or Serum beta-HCG)	X[2]										
UA[4]	X[2]										
PT/INR and PTT	X[2]										
Chemistries[7]	X[2]	X	X	X	X	X	X	X	X	X	X
CBC	X[2]	X	X	X	X	X	X	X	X	X	X
TSH	X[2]			X	X	X	X	X	X	X	X
T/B/NK subsets	X[2]	X	X	X	X	X	X	X	X	X	X
Tumor Markers: Calcitonin and CEA	X[2]	X	X	X	X	X	X	X	X	X	X
Correlative Research Studies (research bloods see **Appendix B**)	X	continue at 3 month intervals									X[8]
Radiological Assessments (MRI or CT Neck, Ch/Abd/Pelvis, Bone Scan) [3]	X	continue at 3 month intervals									
EKG [3]	X	continue at 3 month intervals									X
Biopsy (optional)[8]											
Adverse Events		X	→								
Concomitant Medications		X									

[1] If patient is delayed, subsequent infusion must be at least 18 days later

[2] Must be done within 10 days prior to initiation of study therapy

[3] Must be done within 8 weeks prior to initiation of study therapy, and then will be done every 3 months while patients remain on study

[4] May be omitted if patient is incontinent and cannot provide a urine sample

[5] Baseline/Screening requirements may also be used for Day 1 requirements if logistically necessary

[6] Post-Therapy Assessment done 3 weeks after last treatment when logistically feasible (with a possible extension to 4 weeks if logistically necessary). Patients will be offered enrollment in the 04-C-0274 "Follow-Up Study of Subjects Previously Enrolled in Immunotherapy Studies Utilizing Gene Transfer or other Immunotherapeutic Agents" once off study.

[7] Chemistries: sodium, potassium, chloride, CO2, creatinine, glucose, BUN, albumin, calcium, magnesium, phosphorus, alkaline phosphatase, ALT, AST, total bilirubin, direct bilirubin, LD, total protein, total CK, uric acid

[8] When logistically feasible, pre-treatment and post-treatment samples may be obtained from consenting patients.

3.5 Criteria for Removal from Protocol Therapy and Off Study Criteria

Prior to documenting removal from study, effort must be made to have all subjects complete a safety visit approximately 3-4 weeks following the last dose of study therapy.

3.5.1 Criteria for removal from protocol therapy

- Completion of protocol therapy
- Clinical progression of disease based on increased symptoms or immune related response criteria (irRC) to also be implemented for disease progression as described in **6.3.2**.
- Grade 3 or greater toxicity attributed to treatment that does not resolve to grade 1 within 21 days from time of scheduled treatment.
- Grade 3 or greater autoimmune disease that threatens vital organs.
- Intercurrent illness or medical circumstances. If at any time the constraints of this protocol are detrimental to the patient's health, the patient may be removed from protocol therapy and reasons for withdrawal will be documented.
- Subject decides to withdraw from the study (In this event, the reasons for withdrawal will be documented)
- Investigator discretion
- Positive pregnancy test

3.5.2 Off-Study Criteria

Patients will be removed from the study for the following:

- Subjects proceeds to alternative treatments
- Death
- Patient requests to be taken off study. Reasons for withdrawal will be documented.
- Noncompliance with protocol guidelines (patient removed at discretion of Principal Investigator).
- Investigator decides to end the study
- Screen failure

Patients will be offered enrollment in the 04-C-0274 "Follow-Up Study of Subjects Previously Enrolled in Immunotherapy Studies Utilizing Gene Transfer or other Immunotherapeutic Agents" once off study.

3.5.3 Off Protocol Therapy and Off-Study Procedure

Authorized staff must notify Central Registration Office (CRO) when a subject is taken off protocol therapy and when a subject is taken off-study. A Participant Status Updates Form from

the web site (http://home.ccr.cancer.gov/intra/eligibility/welcome.htm) main page must be completed and sent via encrypted email to: NCI Central Registration Office ncicentralregistration-l@mail.nih.gov.

4 CONCOMITANT MEDICATIONS/MEASURES

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 may 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.

4.1.1 Acceptable Concomitant Medications

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

All concomitant medications received within 28 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered after 30 days after the last dose of trial treatment should be recorded for SAEs a as defined in Section **7.1.5**.

4.1.2 Prohibited Concomitant Medications

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

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab
- Radiation therapy
    - Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed at the investigator's discretion.
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine.

- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.

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

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

4.1.3 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 **3.3.1** 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 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.
- **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	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab (MK-3475) with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic).

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
	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.**	
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.		

5 BIOSPECIMEN COLLECTION

5.1 Collection of Research (Immunologic) Blood Samples (all patients)

The amount of blood that may be drawn from adult patients (i.e., those persons 18 years of age or older) for research purposes shall not exceed 10.5 mL/kg or 550 mL, whichever is smaller, over any eight week period.

5.1.1 Immunologic Parameters (every 3 weeks unless not logistically feasible)

- Leukocyte CD3, CD4, CD8 subsets; CD4:CD8 ratio will be drawn at baseline and at each visit when on treatment (prior to vaccine) and then at follow-up visit while the patient remains on trial
- Additional studies will include but are not limited to quantitative and qualitative assessments of regulatory T-cells, Natural Killers cells, and Myeloid Derived Suppressor Cells.
- Assessment of serum levels of cytokines.
- Immunologic studies will be repeated more frequently if clinically indicated, and any abnormalities potentially related to treatment will be followed until they have resolved, or have been determined not to be treatment-related.
- Peripheral blood mononuclear cells (PBMC):
  Intracellular cytokine staining assays for specific antigens may be done based on preliminary data.
- Phenotypic and functional analysis of immune cell subsets by flow cytometry.

5.1.1.1 Collection of Specimens

6 (10mL) green top sodium heparin tubes for PBMC; 2 (8mL) SST tubes for serum sample.

5.1.2 Natural Killer (NK) CELLS

The number and phenotype of NK cells will be determined by phenotypic analysis of PMBCs stained for CD56, CD3, CD8, and CD16 by flow cytometry.

5.1.3 Immune Subsets

Subsets of immune cells will also be followed in response to treatment.

5.1.4 Regulatory T Cells

Regulatory T cells have been shown to inhibit the activation and function of T cells that participate in antigen-specific immune responses. Higher levels of regulatory T-cells have been reported in the peripheral blood mononuclear cells of patients with several types of tumors. The number and phenotype of regulatory T-cells in peripheral blood mononuclear cells from patients in this study will be determined by 7-color flow cytometry analysis. Cells will be resuspended in staining buffer (phosphate-buffered saline containing 3% fetal bovine serum) and stained for CD4, CD25, CD127, FoxP3, CTLA-4, CD45RA, and CD8. The ratios between regulatory T-cells and CD4 effector cells and the ratios between regulatory T-cells and CD8 Effector cells will also be analyzed.

5.1.5 Additional Assays

Blood samples may be used for additional research studies, which may include one of the following - phenotypic and functional analysis of immune-cell subsets and analyses for cytokines (IFN-γ, IL-10, IL-12, IL-2, IL-4, etc.), chemokines, antibodies related to the tumor or vaccine, tumor associated antigens related to the tumor or the vaccine, and/or other immune response markers.

5.1.6 Biopsy analysis by interventional radiology (Optional).

When logistically feasible, pre-treatment and post-treatment samples may be obtained from consenting patients. Potential analysis could include PD1/PDL1 expression and immune cell infiltration.

5.1.7 Immunohistochemistry

The Laboratory of Pathology and the Warren G. Magnuson Clinical Center will perform Immunohistochemistry on biopsied tissue, if the patient elects to have the procedure. Immunohistochemistry of these tissue specimens will be obtained for CD4, CD8, and FOX-P3. In addition, phenotypic analysis of infiltrating immune cells will be performed.

Immunohistologic grading schema of the lesions

Score	%positive cells of each subtype
0	0
1	1-25%
2	26-50%
3	>50%

All staining will be categorized as being membrane or nuclear

5.2 Sample Storage, Tracking and Disposition

Samples will be ordered in CRIS and tracked through a Clinical Trial Data Management system. Should a CRIS screen not be available, the CRIS downtime procedures will be followed. Samples will not be sent outside NIH without IRB notification and an executed MTA.

5.2.1 Procedures for storage of tissue specimens in the Laboratory of Pathology

Tissues designated for clinical diagnostics are transported to the Laboratory of Pathology (LP) where they are examined grossly and relevant portions are fixed, embedded in paraffin and sectioned and stained for diagnostic interpretation. Unutilized excess tissues are stored for up to three months, in accordance with College of American Pathologists/Joint Commission on Accreditation of Healthcare Organizations (CAP/JCAHO) guidelines, and then discarded.

Following completion of the diagnostic workup, the slides and tissue blocks are stored indefinitely in the LP's clinical archives. All specimens are catalogued and retrieved utilizing the clinical laboratory information systems, in accordance with CAP/JCAHO regulations. The use of any stored specimens for research purposes is only allowed when the appropriate IRB approval has been obtained. In some cases, this approval has been obtained via the original protocol on which the patient was enrolled.

5.2.2 Blood Processing Core - Storage

All samples sent to the Blood Processing Core (BPC) will be barcoded, with data entered and stored in the LABrador (aka LabSamples) utilized by the BPC. This is a secure program, with access to LABrador limited to defined Figg lab personnel, who are issued individual user accounts. Installation of LABrador is limited to computers specified by Dr. Figg. These computers all have a password restricted login screen. All Figg lab personnel with access to patient information annually complete the NIH online Protection of Human Subjects course.

LABrador creates a unique barcode ID for every sample and sample box, which cannot be traced back to patients without LABrador access. The data recorded for each sample includes the patient ID, name, trial name/protocol number, time drawn, cycle time point, dose, material type, as well as box and freezer location. Patient demographics associated with the clinical center patient number are provided in the system. For each sample, there are notes associated with the processing method (delay in sample processing, storage conditions on the ward, etc.).

Barcoded samples are stored in barcoded boxes in a locked freezer at either -20 or -80°C according to stability requirements. These freezers are located onsite in the BPC and offsite at NCI Frederick Central Repository Services (American Type Culture Collection (ATCC)) in Frederick, MD. Visitors to the laboratory are required to be accompanied by laboratory staff at all times.

Access to stored clinical samples is restricted. Samples will be stored until requested by a researcher named on the protocol. All requests are monitored and tracked in LABrador. All researchers are required to sign a form stating that the samples are only to be used for research purposes associated with this trial (as per the IRB approved protocol) and that any unused samples must be returned to the BPC. It is the responsibility of the NCI Principal Investigator to ensure that the samples requested are being used in a manner consistent with IRB approval.

Following completion of this study, samples will remain in storage as detailed above. Access to these samples will only be granted following IRB approval of an additional protocol, granting the rights to use the material.

If, at any time, a patient withdraws from the study and does not wish for their existing samples to be utilized, the individual must provide a written request. Following receipt of this request, the samples will be destroyed (or returned to the patient, if so requested), and reported as such to the IRB. Any samples lost (in transit or by a researcher) or destroyed due to unknown sample integrity (i.e. broken freezer allows for extensive sample thawing, etc.) will be reported as such to the IRB.

Sample barcodes are linked to patient demographics and limited clinical information. This information will only be provided to investigators listed on this protocol, via registered use of the LABrador. It is critical that the sample remains linked to patient information such as race, age, dates of diagnosis and death, and histological information about the tumor, in order to correlate genotype with these variables.

5.2.3 Samples Sent to Clinical Services Program (CSP)

The samples will be processed through:

Clinical Services Program
NCI Frederick Cancer Research and Development Center
PO Box B
Frederick, MD 21702
301-846-1000

On days samples are drawn, Jen Bangh at CSP should be notified (phone: [301] 846-5893; fax [301] 846-6222). She will arrange same-day courier delivery of the specimens.

The research samples will contain labels on the blood tubes that have the patient's initials, date of birth, the assigned protocol, and the date the sample was drawn. The transmittal forms accompanying the samples also contain the same information.

Once a patient's treatment schedule has been determined, it should be faxed to Caroline Jochems at the Laboratory of Tumor Immunology and Biology/ NIH (Fax: [301] 496-2756; phone: [301] 496-9573) for planning purposes.

All data associated with patient samples are protected by a secure database. All samples drawn at the NIH Clinical Center will be transported to the NCI Frederick Central Repository by Leidos couriers.

Samples will be tracked and managed by the Central Repository database. All samples will be stored in liquid nitrogen. These freezers are located at NCI Frederick Central Repository in Frederick, Maryland.

American Type Culture Collection (ATCC) manages the NCI-Frederick Central Repositories under subcontract to Leidos Biomedical Research, Inc. NCI-Frederick Central Repositories store, among other things, biological specimens in support of NIH clinical studies. All specimens are stored in secure, limited access facilities with sufficient security, back up and emergency support capability and monitoring to ensure long-term integrity of the specimens for research.

ATCC's role is limited to clinical research databases and repositories containing patient specimens. ATCC does not conduct nor has any vested interest in research on human subjects, but does provide services and support the efforts of its customers, many of which are involved in research on human subjects.

It is the intent and purpose of ATCC to accept only de-identified samples and sample information. To the limit of our ability, every effort will be made to ensure that protected information is not sent electronically or by hard copy or on vial labels.

Sample data is stored in the BioSpecimen Inventory System II (BSI). This inventory tracking system is used to manage the storage and retrieval of specimens as well as maintain specimen data. BSI is designed for controlled, concurrent access. It provides a real-time, multi-user environment for tracking millions of specimens. The system controls how and in what order database updates and searches are performed. This control prevents deadlocks and race conditions. For security, BSI has user password access, three types of user access levels, and 36 user permissions (levels of access) that can be set to control access to the system functions. BSI provides audit tracking for processes that are done to specimens including shipping, returning to inventory, aliquoting, thawing, additives, and other processes. BSI tracks the ancestry of specimens as they are aliquoted, as well as discrepancies and discrepancy resolution for specimens received by the repository. If a specimen goes out of the inventory, the system maintains data associated with the withdraw request. Vials are labeled with a unique BSI ID which is printed in both eye readable and bar coded format. No patient specific information is encoded in this ID.

Investigators are granted view, input and withdraw authority only for their specimens. They may not view specimen data or access specimens for which they have not been authorized. Access to specimen storage is confined to repository staff. Visitors to the repositories are escorted by repository staff at all times.

5.2.4 Protocol Completion/Sample Destruction

Once primary research objectives for the protocol are achieved, intramural researchers can request access to remaining samples, provided they have an IRB-approved protocol and patient consent.

Samples and associated data will be stored permanently unless the patient withdraws consent. If the patient withdraws consent the participant's data will be excluded from future distributions, but data that have already been distributed for approved research use will not be able to be retrieved. The PI will report destroyed samples to the IRB if samples become unsalvageable or destroyed by environmental conditions (ex. broken freezer or lack of dry ice in shipping container) or if a patient chooses to withdraw his/her consent. Samples will also be reported as lost if they are lost in transit or misplaced by a researcher. Freezer problems, lost samples or other problems associated with samples will also be reported to the IRB, the NCI Clinical Director, and the office of the CCR, NCI.

6 DATA COLLECTION AND EVALUATION

6.1 Data Collection

The PI will be responsible for overseeing entry of data into an in-house password protected electronic system (C3D) and ensuring data accuracy, consistency and timeliness. The principal investigator, associate investigators/research nurses and/or a contracted data manager will assist with the data management efforts. All data obtained during the conduct of the protocol will be kept in secure network drives or in approved alternative sites that comply with NIH security standards. Primary and final analyzed data will have identifiers so that research data can be attributed to an individual human subject participant.

Clinical data will be entered in a secure electronic database, NCI C3D database, and hard copies will be stored in locked, secured areas. Completed eligibility checklists (developed by Central Registration Office, CRO), patient information/registration forms, and blood sample flow sheets will also be stored. Copies of all records of adverse events will be kept in the regulatory binder.

Complete records must be maintained on each patient, including the hospital chart with any supplementary information obtained from outside laboratories, radiology reports, or physician's records. These records will serve as the primary source material that forms the basis for the research record. All relevant data will also be entered in a computer database from which formal analyses will be done.

The primary source documentation will include: on-study information, including patient eligibility data and patient history; flow sheets, records of adverse events, specialty forms for pathology, radiation, or surgery; and off-study summary sheets, including a final assessment by the treating physician.

All adverse events, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed until return to baseline or stabilization of event. Patients will be followed for adverse events for at least 30 days after removal from study treatment or until off-study, whichever comes first.

An abnormal laboratory value will be recorded in the database as an AE **only** if the laboratory abnormality is characterized by any of the following:

- Results in discontinuation from the study
- Is associated with clinical signs or symptoms
- Requires treatment or any other therapeutic intervention
- Is associated with death or another serious adverse event, including hospitalization.
- Is judged by the Investigator to be of significant clinical impact
- If any abnormal laboratory result is considered clinically significant, the investigator will provide details about the action taken with respect to the test drug and about the patient’s outcome.

End of study procedures: Data will be stored according to HHS, FDA regulations, and NIH Intramural Records Retention Schedule as applicable.

Loss or destruction of data: Should we become aware that a major breach in our plan to protect subject confidentiality and trial data has occurred, the IRB will be notified.

6.2 Data Sharing Plans

6.2.1 Human Data Sharing Plan

What data will be shared?

I will share human data generated in this research for future research as follows:

- De-identified data in an NIH-funded or approved public repository.
- De-Identified data in BTRIS (automatic for activities in the Clinical Center)
- De-identified or identified data with approved outside collaborators under appropriate agreements.

How and where will the data be shared?

Data will be shared through:

- An NIH-funded or approved public repository. Insert name or names: clinicaltrials.gov .
- BTRIS (automatic for activities in the Clinical Center)
- Approved outside collaborators under appropriate individual agreements.
- Publication and/or public presentations.

When will the data be shared?

- Before publication.
- At the time of publication or shortly thereafter.

6.2.2 Genomic Data Sharing Plan

No genomic data will be gathered as part of this study.

6.3 Response Criteria

For the purposes of this study, patients should be re-evaluated for response per the study calendar (**3.4**). In addition to a baseline scan, confirmatory scans should also be obtained not less than 4 weeks following initial documentation of objective response.

Responses will be assessed using both serum calcitonin levels and imaging using Immune Related Response Criteria below.

6.3.1 Serum Calcitonin

For calcitonin, response assessment, the baseline calcitonin value will be established prior to treatment. If multiple values have been obtained, the most recent value will be considered the baseline unless the primary investigator feels that the value is unreliable. In this case a note will document the reason for not using that value at enrollment and identification of an alternative baseline (obtained within 8 weeks of enrollment) will be used.

In order to be considered to have a "Calcitonin Response" patients must have a $\geq$50% decline from designated baseline value that is then confirmed on a subsequent serum calcitonin assessment at least one week later.

6.3.2 Imaging

Immune Related Response Criteria

Because of direct clinical observations of immune cell influx into tumor causing enlargement in some patients prior to sustained response, recently it has been suggested that clinical trials involving the use of immunotherapy use alternative guidelines, called immune related response criteria (irRC) to determine radiographic response or progression after therapy[22]. These recommendations have been used in recent clinical trials. One study of 227 subjects with metastatic melanoma showed that the approximately 10% of patients who had PD by modified WHO criteria but either of CR, PR or SD by irRC had a similar overall survival as those patients who had SD, PR or CR by both criteria. The irRC was created using bidimensional measurements (as previously widely used in the WHO criteria). We have taken the concepts of the irRC and combined them with the recently revised RECIST 1.1[23] to come up with the modified irRC used in this protocol. Consistent with the irRC, the main changes from RECIST 1.1 are (a) a requirement for confirmation of both progression and response by imaging at least 4 weeks after initial imaging and (b) not automatically calling the appearance of new lesions progressive disease if the total measurable tumor burden has not met criteria for progressive disease.

For immune-related response criteria (irRC), only index and measurable new lesions are taken into account. At baseline tumor assessment on this trial, target lesions will be measured along the longest axis and the measurements will be summed, called sum of largest diameter (SLD). These lesions must be a minimum of 10mm per lesion, maximum of 5 target lesions, maximum of 2 per organ system. At each subsequent tumor assessment, the unidimensional measurement of target lesions and of new measureable lesions are added together to provide the total tumor burden: As per the modified definitions below, all responses and progression except stable

disease (SD) require confirmation on a consecutive scan at least 4 weeks from the initial observation).

Definitions of irRC:

Response	**irRC**
New measurable lesions	**Incorporated into tumor burden**
New non-measurable lesions	**Do not define progression (but precludes irCR)**
Non-index lesions	Contributes to defining irCR (complete disappearance required)
Overall irCR	100% disappearance of all lesions, whether measurable or not, and no new lesions, in two consecutive observations not less than 4 wks from the date first documented. All measurable lymph nodes also must have reduction in short axis to <10mm.
Overall irPR	≥ 30% decrease in SLD compared with baseline confirmed by a consecutive assessment at least 4 wk after first documentation
Overall irSD	Not meeting criteria for irCR or irPR, in absence of irPD: 30% decrease in SLD compared with baseline cannot be established nor 20% increase compared with nadir.
Overall irPD	At least 20% increase in SLD compared with nadir (minimum recorded tumor burden) and an increase of at least 5mm over the nadir, confirmed by a repeat, consecutive observations at least 4 wk from the date first documented.

Overall responses derived from changes in index, non-index and new lesions as demonstrated in the following table:

Measurable response	**Non-measurable response**		**Overall response using irRC**
Index and new, measurable lesions (tumor burden)* %	**Non-index lesions**	**New, non-measurable lesions**	
Decrease 100	Absent	Absent	irCR[&]
Decrease 100	Stable	Any	irPR[&]
Decrease 100	Unequivocal progression	Any	irPR[&]
Decrease ≥ 30%	Absent / Stable	Any	irPR[&]
Decrease ≥ 30%	Unequivocal progression	Any	irPR[&]

Decrease < 30 to increase < 20	Absent / Stable	Any	irSD
Decrease < 30 to increase < 20	Unequivocal progression	Any	irSD
Increase ≥ 20	Any	Any	irPD

* Decreases assessed relative to baseline

[&] Assuming response (irCR) and progression (irPD) are confirmed by a second, consecutive assessment at least 4 weeks apart.

6.3.3 Disease Parameters

Evaluable disease: Disease that can be evaluated on imaging but does not meet the measurable disease criteria below.

Measurable disease: Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded):

- By chest x-ray: ≥20 mm;
- By CT scan:
    - Scan slice thickness 5 mm or under: as ≥10 mm
    - Scan slice thickness >5 mm: double the slice thickness

With calipers on clinical exam: ≥10 mm. Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

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

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

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

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on

occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

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

6.3.4 Methods for Evaluation of Measurable Disease

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

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

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

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

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

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

PET-CT: At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

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

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

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

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

FDG-PET: While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
c. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively

described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

6.3.5 Duration of Response

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

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

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

6.3.6 Progression-Free Survival

PFS is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first.

6.4 Toxicity Criteria

The following adverse event management guidelines are intended to ensure the safety of each patient while on the study. The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40).

7 SAFETY REPORTING REQUIREMENTS/DATA AND SAFETY MONITORING PLAN

7.1 Definitions

7.1.1 Adverse Event

Any untoward medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in research, whether or not considered related to the subject's participation in the research.

7.1.2 Suspected adverse reaction

Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

7.1.3 Unexpected adverse reaction

An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application. "Unexpected" also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

7.1.4 Serious

An Unanticipated Problem or Protocol Deviation is serious if it meets the definition of a Serious Adverse Event or if it compromises the safety, welfare or rights of subjects or others.

7.1.5 Serious Adverse Event

An adverse event or suspected adverse reaction is considered serious if in the view of the investigator or the sponsor, it results in any of the following:

- Death,
- A life-threatening adverse drug experience
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect.
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

7.1.6 Disability

A substantial disruption of a person's ability to conduct normal life functions.

7.1.7 Life-threatening adverse drug experience

Any adverse event or suspected adverse reaction that places the patient or subject, in the view of the investigator or sponsor, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that had it occurred in a more severe form, might have caused death.

7.1.8 Protocol Deviation (NIH Definition)

Any change, divergence, or departure from the IRB-approved research protocol.

7.1.9 Non-compliance (NIH Definition)

The failure to comply with applicable NIH Human Research Protections Program (HRPP) policies, IRB requirements, or regulatory requirements for the protection of human research subjects.

7.1.10 Unanticipated Problem

Any incident, experience, or outcome that:

- Is unexpected in terms of nature, severity, or frequency in relation to

  (a) the research risks that are described in the IRB-approved research protocol and informed consent document; Investigator's Brochure or other study documents, and

  (b) the characteristics of the subject population being studied; **AND**
- Is related or possibly related to participation in the research; **AND**
- Suggests that the research places subjects or others at a *greater risk of harm* (including physical, psychological, economic, or social harm) than was previously known or recognized.

7.2 NCI-IRB and Clinical Director (CD) Reporting

7.2.1 NCI-IRB and NCI CD Expedited Reporting of Unanticipated Problems and Deaths

The Protocol PI will report in the NIH Problem Form to the NCI-IRB and NCI CD:

- All deaths, except deaths due to progressive disease
- All Protocol Deviations
- All Unanticipated Problems
- All non-compliance

Reports must be received within 7 days of PI awareness via iRIS.

7.2.2 NCI-IRB Requirements for PI Reporting at Continuing Review

The protocol PI will report to the NCI-IRB:

1. A summary of all protocol deviations in a tabular format to include the date the deviation occurred, a brief description of the deviation and any corrective action.
2. A summary of any instances of non-compliance
3. A tabular summary of the following adverse events:
   - All Grade 2 **unexpected** events that are possibly, probably or definitely related to the research;
   - All Grade 3 and 4 events that are possibly, probably or definitely related to the research;
   - All Grade 5 events regardless of attribution;
   - All Serious Events regardless of attribution.

   NOTE: Grade 1 events are not required to be reported.

7.3 Safety Reporting Criteria to the Pharmaceutical Collaborator

7.3.1 Serious Adverse Events

The investigator should submit all serious adverse events on a Medwatch 3500 Form within 2 working days of receipt to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215-661-6229)

7.3.2 Reporting of Overdose

All reports of overdose with and without an adverse event must be reported within 2 working days of receipt to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215-661-6229)

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

7.3.3 Reporting of Pregnancy and Lactation

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 manufacturer'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 2 working days of receipt to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215-661-6229).

7.4 Data and Safety Monitoring Plan

7.4.1 Principal Investigator/Research Team

The clinical research team will meet on a regular basis at least monthly when patients are being actively treated on the trial to discuss each patient. Decisions about dose level enrollment and dose escalation if applicable will be made based on the toxicity data from prior patients.

All data will be collected in a timely manner and reviewed by the principal investigator or a lead associate investigator. Adverse events will be reported as required above. Any safety concerns, new information that might affect either the ethical and or scientific conduct of the trial, or protocol deviations will be immediately reported to the IRB using iRIS.

The principal investigator will review adverse event and response data on each patient to ensure safety and data accuracy. The principal investigator will personally conduct or supervise the investigation and provide appropriate delegation of responsibilities to other members of the research staff.

8 STATISTICAL CONSIDERATIONS

The primary objective of this trial is to determine whether administering a PD1 inhibitor to patients with medullary thyroid cancer will permit a modest fraction to be able to experience a 50% or greater decline in calcitonin levels or experience a clinical response by partial/complete response on imaging.

Patients on this trial will be enrolled into two cohorts: patients who have previously received vaccine and patients who have not previously received vaccine. The results from each cohort will be considered individually.

In each cohort, the trial will be conducted as a single stage pilot trial of 15 evaluable patients. It is expected that this regimen will result in a limited fraction of patients who experience a 50% or greater decline in calcitonin levels or experience a clinical response by partial/complete response on imaging. If the true probability that patients will experience a 50% decline in calcitonin or respond is 10%, there is only 5.6% probability or having 4 or more of 15 do so, while if the true probability is 40% or more, there is 90.9% or greater probability of observing 4 or more who experience this decline or respond. Thus, observing 4 or more with this decline or a response in a cohort is more likely to be associated with a modest fraction with 50% or greater decline in calcitonin levels or respond than if fewer patients in a cohort experience this decline or respond.

A 95% confidence interval will also be formed about the observed proportion of patients who experience a 50% or greater decline or respond, and the actual decline percentages for patients

on both cohorts will be reported descriptively, as well as the fraction who experience a clinical response. With limited numbers of patients in this trial, there will be low power to do a formal comparison of the two cohorts; information about the proportion with substantial declines or responses in either cohort may be used to guide development of future trials using this approach.

It is anticipated that 1 patient per month may enroll onto this trial. Thus, to obtain 30 evaluable patients, approximately 2 to 3 years of accrual is anticipated. In order to allow for a small number of inevaluable patients, the accrual ceiling will be set to 32 patients.

9 COLLABORATIVE AGREEMENTS

9.1 Clinical Trials Agreement (CTA)

This study will be conducted with Merck as part of a Clinical Trials Agreement (CTA), CTA# 01054-17.

10 HUMAN SUBJECTS PROTECTIONS

10.1 Rationale For Subject Selection

This study will enroll a minimally symptomatic adult population with medullary thyroid cancer. Preliminary data discussed in the background of the protocol suggests the potential benefit of immunotherapy in these patients.

10.2 Participation of Children

Patients under the age of 18 will not be eligible to enroll on this protocol due to unknown effects of this protocol therapy in this age group with medullary thyroid cancer.

10.3 Participation of Subjects Unable to Give Consent

Adults unable to give consent are excluded from enrolling in the protocol. However, re-consent may be necessary and there is a possibility, though unlikely, that subjects could become decisionally impaired. For this reason and because there is a prospect of direct benefit from research participation (section **10.5**), all subjects ≥ age 18 will be offered the opportunity to fill in their wishes for research and care, and assign a substitute decision maker on the "NIH Advance Directive for Health Care and Medical Research Participation" form so that another person can make decisions about their medical care in the event that they become incapacitated or cognitively impaired during the course of the study. Note: The PI or AI will contact the NIH Ability to Consent Assessment Team for evaluation. For those subjects that become incapacitated and do not have pre-determined substitute decision maker, the procedures described in MAS Policy 87-4 for appointing a surrogate decision maker for adult subjects who are (a) decisionally impaired, and (b) who do not have a legal guardian or durable power of attorney, will be followed.

10.4 Evaluation of Benefits and Risks/Discomforts

The potential benefits of this protocol therapy remain unclear in this population of patients, but preliminary data described in the background suggests the potential for benefit in some patients. The potential side effect profile of pembrolizumab is described in Section **11**.

10.4.1 Optional Biopsies

All care will be taken to minimize risks that may be incurred by tumor sampling. However, there are procedure-related risks (such as bleeding, infection and visceral injury) that will be explained fully during informed consent. If patients suffer any physical injury as a result of the biopsies, immediate medical treatment is available at the NCI's Clinical Center in Bethesda, Maryland.

Although no compensation is available, any injury will be fully evaluated and treated in keeping with the benefits or care to which patients are entitled under applicable regulations.

Some biopsies may be performed with CT guidance. If that is the case, then this research study involves exposure to radiation from up to 2 CT scans, at baseline prior to starting treatment and at the end of treatment (at 2 years). The effective dose per one CT scan will be 0.77 rem. This is below the guideline of 5.0 rem per year allowed for research subjects by the NIH Radiation Safety Committee.

10.5 Risks/Benefits Analysis

This study will enroll a minimally symptomatic adult population with medullary thyroid cancer. These patients are generally monitored in conventional practice at this stage as the lack of substantial symptoms from disease negates the need for FDA-approved therapies which are often accompanied by toxicities. Although immune related adverse events are possible with this study, they are likely manageable and will not substantially impact the quality of life of these patients. The potential benefits of pembrolizumab have yet to be determined in medullary thyroid cancer, although preliminary data from a small number of patients described in the background is hypothesis-generating. Thus in a risk reward analysis (a discussion that will be part of the informed consent process with each patient) this study allows the patients to have an opportunity to try a modern immunotherapeutic agent that is FDA approved for other cancers during a therapeutic window of opportunity.

10.6 Consent Process and Documentation

The investigational nature and objectives of this trial, the procedures involved, and their attendant risks and discomforts, potential benefits, and potential alternative therapies will be explained to the patient and a signed informed consent document obtained. All associate investigators who have clinical privileges listed in this protocol are permitted to obtain informed consent. For the optional biopsy for research in the protocol, the patient will consent at the time of the procedure. If the patient refuses the optional biopsy at that time, the refusal will be documented in the medical record and in the research record.

10.6.1 Telephone Re-Consent Procedure

Re-consent on this study may be obtained via telephone according to the following procedure: the informed consent document will be sent to the subject. An explanation of the study will be provided over the telephone after the subject has had the opportunity to read the consent form. The subject will sign and date the informed consent. A witness to the subject's signature will sign and date the consent. The original informed consent document will be sent back to the consenting investigator who will sign and date the consent form with the date the consent was obtained via telephone. A fully executed copy will be returned via mail for the subject's records. The informed consent process will be documented on a progress note by the consenting investigator and a copy of the informed consent document will be kept in the subject's research record.

10.6.2 Informed Consent of Non-English Speaking Subjects

If there is an unexpected enrollment of a research participant for whom there is no translated extant IRB approved consent document, the principal investigator and/or those authorized to obtain informed consent will use the Short Form Oral Consent Process as described in MAS Policy M77-2, OHSRP SOP 12, 45 CFR 46.117 (b) (2), and 21 CFR 50.27 (b) (2). The summary that will be used is the English version of the extant IRB approved consent document. Signed copies of both the English version of the consent and the translated short form will be given to the subject or their legally authorized representative and the signed original will be filed in the medical record.

Unless the PI is fluent in the prospective subject's language, an interpreter will be present to facilitate the conversation (using either the long translated form or the short form). Preferably someone who is independent of the subject (i.e., not a family member) will assist in presenting information and obtaining consent. Whenever possible, interpreters will be provided copies of the relevant consent documents well before the consent conversation with the subject (24 to 48 hours if possible).

We request prospective IRB approval of the use of the short form process for non-English speaking subjects and will notify the IRB at the time of continuing review of the frequency of the use of the Short Form.

10.7 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) has a congenital or acquired condition that prevents childbearing.

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

(1) practice abstinence† from heterosexual activity;

OR

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

Acceptable methods of contraception are‡:

Single method (one of the following is acceptable):

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

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

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

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

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

country/region.

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

10.8 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 study PI and to Merck without delay and within 24 hours to the study PI 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 PI will make every effort to obtain permission to follow the outcome of the pregnancy and the condition of the fetus or newborn. If a male subject impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to the study PI and to Merck and followed as described above and in Section **7.3.3**.

10.9 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.

11 PHARMACEUTICAL INFORMATION

11.1 Pembrolizumab (MK-3475)

11.1.1 Source

Pembrolizumab will be provided to the NCI pharmacy as part of a clinical trial agreement.

There will be no IND obtained for the use of Pembrolizumab in this study. This study meets the criteria for exemption for an IND as this investigation is not intended to support a new indication for use or any other significant change to the labeling; the drug is already approved and marketed and the investigation is not intended to support a significant change in advertising; and the investigation does not involve a route of administration or dosage level in use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product.

11.1.2 Toxicity

- Immune-mediated pneumonitis, including fatal cases, occurred in patients receiving pembrolizumab. Pneumonitis occurred in 32 (2.0%) of 1567 patients, including Grade 1 (0.8%), 2 (0.8%), and 3 (0.4%) pneumonitis. Monitor patients for signs and symptoms of pneumonitis. Evaluate suspected pneumonitis with radiographic imaging. Administer corticosteroids for Grade 2 or greater pneumonitis. Withhold pembrolizumab for Grade 2; permanently discontinue pembrolizumab for Grade 3 or 4 or recurrent Grade 2 pneumonitis.
- Immune-mediated colitis occurred in 31 (2%) of 1567 patients, including Grade 2 (0.5%), 3 (1.1%), and 4 (0.1%) colitis. Monitor patients for signs and symptoms of colitis. Administer corticosteroids for Grade 2 or greater colitis. Withhold pembrolizumab for Grade 2 or 3; permanently discontinue pembrolizumab for Grade 4 colitis.
- Immune-mediated hepatitis occurred in 16 (1%) of 1567 patients, including Grade 2 (0.1%), 3 (0.7%), and 4 (0.1%) hepatitis. Monitor patients for changes in liver function. Administer corticosteroids for Grade 2 or greater hepatitis and, based on severity of liver enzyme elevations, withhold or discontinue pembrolizumab.
- Hypophysitis occurred in 13 (0.8%) of 1567 patients, including Grade 2 (0.3%), 3 (0.3%), and 4 (0.1%) hypophysitis. Monitor patients for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency). Administer corticosteroids and hormone replacement as clinically indicated. Withhold pembrolizumab for Grade 2; withhold or discontinue for Grade 3 or 4 hypophysitis.
- Hyperthyroidism occurred in 51 (3.3%) of 1567 patients, including Grade 2 (0.6%) and 3 (0.1%) hyperthyroidism. Hypothyroidism occurred in 127 (8.1%) of 1567 patients, including Grade 3 (0.1%) 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. Administer replacement hormones for hypothyroidism and manage hyperthyroidism with thionamides and beta-blockers as appropriate. Withhold or discontinue pembrolizumab® (pembrolizumab) for Grade 3 or 4 hyperthyroidism.
- Type 1 diabetes mellitus, including diabetic ketoacidosis, occurred in 3 (0.1%) of 2117 patients. Monitor patients for hyperglycemia or other signs and symptoms of diabetes. Administer insulin for type 1 diabetes, and withhold pembrolizumab and administer anti-hyperglycemics in patients with severe hyperglycemia.
- Immune-mediated nephritis occurred in 7 (0.4%) of 1567 patients, including Grade 2 (0.2%), 3 (0.2%), and 4 (0.1%) nephritis. Monitor patients for changes in renal function. Administer corticosteroids for Grade 2 or greater nephritis. Withhold pembrolizumab for Grade 2; permanently discontinue pembrolizumab for Grade 3 or 4 nephritis.
- Other clinically important immune-mediated adverse reactions can occur. For suspected immune-mediated adverse reactions, ensure adequate evaluation to confirm etiology or exclude other causes. Based on the severity of the adverse reaction, withhold

pembrolizumab and administer corticosteroids. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Based on limited data from clinical studies in patients whose immune-related adverse reactions could not be controlled with corticosteroid use, administration of other systemic immunosuppressants can be considered. Resume pembrolizumab when the adverse reaction remains at Grade 1 or less following corticosteroid taper. Permanently discontinue pembrolizumab for any Grade 3 immune-mediated adverse reaction that recurs and for any life-threatening immune-mediated adverse reaction.

- The following clinically significant, immune-mediated adverse reactions occurred in less than 1% (unless otherwise indicated) of 1567 patients: arthritis (1.6%), exfoliative dermatitis, bullous pemphigoid, uveitis, myositis, Guillain-Barré syndrome, myasthenia gravis, vasculitis, pancreatitis, hemolytic anemia, and partial seizures arising in a patient with inflammatory foci in brain parenchyma.
- Severe and life-threatening infusion-related reactions have been reported in 3 (0.1%) of 2117 patients. Monitor patients for signs and symptoms of infusion-related reactions including rigors, chills, wheezing, pruritus, flushing, rash, hypotension, hypoxemia, and fever. For Grade 3 or 4 reactions, stop infusion and permanently discontinue pembrolizumab.
- Based on its mechanism of action, pembrolizumab can cause fetal harm when administered to a pregnant woman. If used during pregnancy, or if the patient becomes pregnant during treatment, apprise the patient of the potential hazard to a fetus. Advise females of reproductive potential to use highly effective contraception during treatment and for 4 months after the last dose of pembrolizumab.
- In Trial 6, pembrolizumab was discontinued due to adverse reactions in 9% of 555 patients; adverse reactions leading to discontinuation in more than one patient were colitis (1.4%), autoimmune hepatitis (0.7%), allergic reaction (0.4%), polyneuropathy (0.4%), and cardiac failure (0.4%). Adverse reactions leading to interruption of pembrolizumab occurred in 21% of patients; the most common (≥1%) was diarrhea (2.5%). The most common adverse reactions with pembrolizumab vs ipilimumab were fatigue (28% vs 28%), diarrhea (26% with pembrolizumab), rash (24% vs 23%), and nausea (21% with pembrolizumab). Corresponding incidence rates are listed for ipilimumab only for those adverse reactions that occurred at the same or lower rate than with pembrolizumab.
- In Trial 2, pembrolizumab was discontinued due to adverse reactions in 12% of 357 patients; the most common (≥1%) were general physical health deterioration (1%), asthenia (1%), dyspnea (1%), pneumonitis (1%), and generalized edema (1%). Adverse reactions leading to interruption of pembrolizumab occurred in 14% of patients; the most common (≥1%) were dyspnea (1%), diarrhea (1%), and maculo-papular rash (1%). The most common adverse reactions with pembrolizumab vs chemotherapy were fatigue (43% with pembrolizumab), pruritus (28% vs 8%), rash (24% vs 8%), constipation (22% vs 20%), nausea (22% with pembrolizumab), diarrhea (20% vs 20%), and decreased appetite (20% with pembrolizumab). Corresponding incidence rates are listed for

chemotherapy only for those adverse reactions that occurred at the same or lower rate than with pembrolizumab.

- No formal pharmacokinetic drug interaction studies have been conducted with pembrolizumab.
- It is not known whether pembrolizumab is excreted in human milk. Because many drugs are excreted in human milk, instruct women to discontinue nursing during treatment with pembrolizumab and for 4 months after the final dose.
- Safety and effectiveness of pembrolizumab have not been established in pediatric patients.

11.1.3 Formulation and preparation

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

11.1.4 Stability and Storage

- 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.
- The product does not contain a preservative.
- Store the reconstituted and diluted solution from the pembrolizumab 50 mg vial either:
    - At room temperature for no more than 6 hours from the time of reconstitution. This includes room temperature storage of reconstituted vials, storage of the infusion solution in the IV bag, and the duration of infusion.
    - Under refrigeration at 2°C to 8°C (36F to 46F) for no more than 24 hours from the time of reconstitution. If refrigerated, allow the diluted solution to come to room temperature prior to administration.
- Store the diluted solution from the pembrolizumab 100 mg/4 mL vial either:

  - At room temperature for no more than 6 hours from the time of dilution. This includes room temperature storage of the infusion solution in the IV bag, and the duration of infusion.
  - Under refrigeration at 2°C to 8°C (36F to 46F) for no more than 24 hours from the time of dilution. If refrigerated, allow the diluted solution to come to room temperature prior to administration.
- Do not freeze.

11.1.5 Administration procedures

Reconstitution of pembrolizumab for Injection (Lyophilized Powder)

- Pembrolizumab is administered through a 0.2 to 5 micron sterile, nonpyrogenic, low-protein binding inline or add-on filter. Do not infuse other mediations through the same infusion line.
- Add 2.3 mL of Sterile Water for Injection, USP by injecting the water along the walls of the vial and not directly on the lyophilized powder (resulting concentration 25mg/mL).
- Slowly swirl the vial. Allow up to 5minutes for the bubbles to clear. Do not shake the vial
- Preparation for Intravenous Infusion
- Visually inspect the solution for particulate matter and discoloration prior to administration. The solution is clear to slightly opalescent, colorless to slightly yellow. Discard the vial if visible particles are observed.
- Dilute pembrolizumab injection (solution) or reconstituted lyophilized powder prior to intravenous administration.
- Withdraw the required volume from the vial(s) of pembrolizumab and transfer into an intravenous (IV) bag containing 0.9% Sodium Chloride Injection, USP or 5%
- Dextrose Injection, USP. Mix diluted solution by gentle inversion. The final concentration of the diluted solution should be between 1mg/mL to 10mg/mL.
- Discard any unused portion left in the vial.

11.1.6 Incompatibilities

No formal pharmacokinetic drug interaction studies have been conducted with pembrolizumab.

11.1.7 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.

11.1.8 Returns and Reconciliation

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

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

12 APPENDIX A: PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
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).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active 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.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

13 APPENDIX B: INSTRUCTIONS FOR PRE-STUDY AND FOLLOW-UP BLOOD TESTS

Blood Studies	Blood Tube/Comments	Destination
CBC, with differential	1 purple top	Clinical Center Lab Bldg. 10
BUN, Creatinine SGOT, Alk. Phos, Bilirubin, Albumin (chem. 20), TSH	1 gold top	Hem/Onc Lab Bldg. 10
Serum for HIV Antibody	1 gold top HIV Consent	Hem/Onc Lab Bldg. 10
Immunology Assays	6 10-cc green tops 2 SST (tiger) top tubes	NCI-Frederick (Leidos) (1-301-846-5893)
T/B/NK (lymphocyte subsets)	1 purple top	Clinical Center Lab Bldg 10

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