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“Phase II Trial of Pembrolizumab in Metastatic or Locally Advanced Anaplastic/Undifferentiated Thyroid Cancer”

aka “Pembrolizumab in Anaplastic/Undifferentiated Thyroid Cancer”

28 September 2019 (version 3)

UTSouthwestern Harold C. Simmons Comprehensive Cancer Center | NCI CCC

Phase II Trial of Pembrolizumab in Metastatic or Locally Advanced Anaplastic/Undifferentiated Thyroid Cancer

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Study Drug: Pembrolizumab

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IND Holder Name: Dr. Saad Khan, UT Southwestern Medical Center

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Signature Page

Protocol Version 3.0, September 28, 2019

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

Principal Investigator (PI) Name:_____

PI Signature: _____

Date:_____

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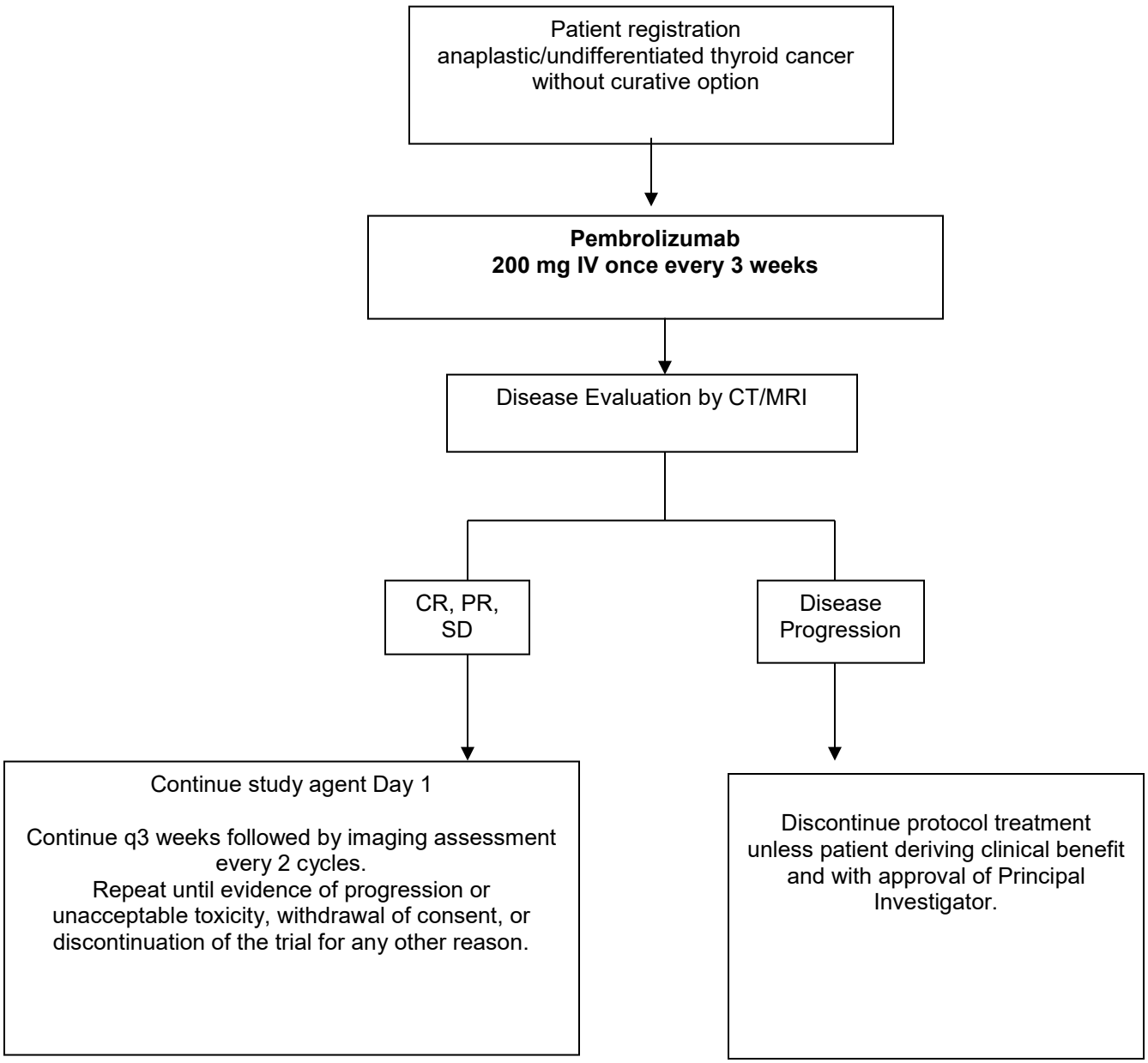
LIST OF ABBREVIATIONS (EXAMPLES)

AE	Adverse Event
ALT	Alanine Aminotransferase
ALC	Absolute Lymphocyte Count
ALK	Anaplastic lymphoma kinas
ASCO	American Society of Clinical Oncology
AST	Aspartate Aminotransferase
ATC	Anaplastic Thyroid Cancer
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CMP	Comprehensive Metabolic Panel
CR	Complete Response
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose Limiting Toxicity
DOT	Disease Oriented Team
DSMB	Data and Safety Monitoring Board
ECOG	Eastern Cooperative Oncology Group
FDA	Food and Drug Administration
GCP	Good Clinical Practice
H&P	History & Physical Exam
HRPP	Human Research Protections Program
IHC	Immunohistochemistry
IND	Investigational New Drug
IV (or iv)	Intravenously
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
ORR	Overall Response Rate
OS	Overall Survival
PBMCs	Peripheral Blood Mononuclear Cells
pCR	Pathologic Complete Response
PD	Progressive Disease
PET	Positron Emission Tomography
PFS	Progression Free Survival
p.o.	peros/by mouth/orally
PR	Partial Response
RCB	Residual Cancer Burden
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SCCC	Simmons Comprehensive Cancer Center
SD	Stable Disease
SGOT	Serum Glutamic Oxaloacetic Transaminase

SPGT	Serum Glutamic Pyruvic Transaminase
WBC	White Blood Cells

STUDY SCHEMA



STUDY SUMMARY

Title	Phase II trial of Pembrolizumab in metastatic or locally advanced anaplastic/undifferentiated thyroid cancer
Short Title	Pembrolizumab in anaplastic/undifferentiated thyroid cancer
Protocol Number	*Insert from PRMC Approval Letter*
Phase	Phase 2
Methodology	Open label, non-randomized single agent trial
Study Duration	2 years
Study Center(s)	Multicenter, additional 3 centers expected
Objectives	Response rate of pembrolizumab in anaplastic/undifferentiated thyroid cancer
Number of Subjects	20
Diagnosis and Main Inclusion Criteria	Anaplastic/undifferentiated thyroid cancer that is metastatic or locally advanced with no curative treatment options.
Study Product(s), Dose, Route, Regimen	Pembrolizumab (Keytruda-Merck) 200 mg, given IV every 3 weeks.
Duration of administration	Until evidence of progression, intolerance of treatment, withdrawal of consent or death
Reference therapy	Historical controls, no established chemotherapy options in this disease proven to show survival benefit
Statistical Methodology	Sample size calculated on the basis of tumor response rate of patients treated on this protocol compared to published response rates. Kaplan Meier Methods will be used to estimate progression-free survival, overall survival and response duration.

1.0 BACKGROUND AND RATIONALE

1.1 Disease Background

1.1.1 Anaplastic Thyroid Cancer

Anaplastic thyroid cancer (ATC) is an undifferentiated tumor of thyroidal follicular epithelium. Although not as common as differentiated thyroid cancers, ATC has much higher disease specific mortality, approaching 100% [1]. In fact, despite accounting for less that 5% of all thyroid cancer diagnoses, ATC leads to more than half of the 1200 deaths from thyroid cancer every year in the United States [2, 3].

Forty six percent of patients present with distant metastases, and almost 70% demonstrate metastases at some stage of the disease [3]. All staging for anaplastic thyroid cancer is as stage IV [3], given its aggressive nature and propensity for metastasis. Even with the most aggressive existing multimodality therapy involving surgery, radiation and chemotherapy, most patients do not derive consistent, sustained benefit in outcomes and survival. Median overall survival remains 3-4 months, with 90% of patients dead at 1 year from diagnosis [3]. Patients often suffer from distant metastases even after local therapy is completed, demonstrating the inadequacy of treatment. Lung, brain and bone metastases are common as well as significant airway compromise and suffocation even after tracheostomy.

1.1.2 Treatment for Anaplastic Thyroid Cancer-Chemotherapy

Doxorubicin is the only approved chemotherapy for anaplastic thyroid cancer [4], and is often combined with radiation or surgery as part of multi-modality therapy. No randomized trial has demonstrated improved statistically significant survival or better quality of life in patients treated with any current therapy [4].

Given the poor prognosis, guidelines from the American Thyroid Association as well as the National Comprehensive Cancer Network recommend all patients should be treated as part of a clinical trial regardless of stage [4, 5].

This treatment protocol aims to offer a new therapy for patients with anaplastic thyroid cancer who would otherwise have very poor treatment options and outcome.

1.1.3 Treatment for Anaplastic Thyroid Cancer-Targeted Therapy and Clinical Trials

There are currently no approved and no commonly employed targeted therapies in anaplastic thyroid cancer. This is an area of urgent need for patients, not just for approved treatments but also rationally-designed clinical trials designed specifically for ATC.

Newer agents have been tested in patients with ATC, but currently none have been approved for any stage of therapy for patients in the US. Fosbretabulin is a novel tubulin binding compound that demonstrated activity in ATC [6]. A Phase III trial randomized ATC patients to fosbretabulin or placebo. These patients had previously received carboplatin and paclitaxel treatment and 55% of them had undergone surgical resection [7]. The arm containing the experimental drug had 33.3% survival at one year vs 7% for the carboplatin and paclitaxel alone arm. Although not powered to detect differences in survival, the median survival for the standard arm was reported as 4 months for the control arm versus 8.4 months for the fosbretabulin arm.

Sorafenib has demonstrated some activity in multi-institution, small studies. In 20 patients treated with sorafenib, 2 patients demonstrated a partial response [8]. Sorafenib is currently not listed as a recommended regimen in the NCCN guidelines for anaplastic thyroid cancer, nor in the ATA guidelines for Anaplastic Thyroid Cancer.

Clinical trials for this disease are also extremely rare, leaving patients with very limited treatment options. Patients diagnosed with anaplastic thyroid cancer have a very high likelihood of dying because of their disease. As such there is a clear need for improving therapy for anaplastic thyroid cancer.

1.1.4 Immune checkpoints in cancer

Cancer cells can evade destruction by the immune system, and can gain the ability to circumvent the usual immune checkpoints [9, 10]. The programmed death 1 (PD-1) receptor and its ligands appear to play a role in the tumor cells evading immune-mediated destruction. PD-1 is an immunoinhibitory receptor that is expressed on B/T cells, tumor infiltrating lymphocytes, monocytes and NK cells [11].

The binding of PD-1 to one of its ligands PD-L1 or PD-L2 results in inhibition of cytotoxic T-cell responses [12]. Pembrolizumab is a monoclonal antibody against PD-1 which disrupts ligand binding and T cell inhibitory signals, resulting in increased tumor recognition by cytotoxic T-cells[13].

Higher levels of PD-L1 are associated with an increased response rate of lung cancer to anti-PD-1 therapy [13]. PD-L1 overexpression is associated with more aggressive disease in papillary thyroid cancer [14], but has not been similarly evaluated in anaplastic thyroid cancer. In a small series, PD-L1 expression was seen in 3 out of 13 anaplastic thyroid cancer patients [15], though whether this represents the true frequency of PD-L1 overexpression is unknown. It is also unknown whether PD-L1 expression correlates with response to anti-PD-1 agents in thyroid cancer.

1.1.5 Molecular abnormalities in anaplastic thyroid cancer

The frequency of mutations in anaplastic thyroid cancer/undifferentiated thyroid cancer is not well-defined. The impact of mutations in ATC may be to alter its natural history and may also be associated with differential responses to immune based therapy.

Experiments have been done to determine the genetic drivers of malignancy in aggressive thyroid cancer. In anaplastic thyroid cancer (ATC) collected from patient samples, mutations in the kinase domain of *ALK* have been characterized in 11% [16]. In this study of ATC, two exons in the tyrosine kinase domain were sequenced and novel mutations were found in both exon 23 and 25. Both mutations led to increased tyrosine kinase activity of *ALK*.

These mutations were associated with activation of the PI3kinase pathway as well as high phosphorylation levels of Akt and ERK, suggesting that they contributed to malignant behavior. These novel *ALK* mutations were transfected into wild type *ALK* cells, and stimulated cell transformation and invasion as possible mechanism of malignancy, the frequency of *ALK* mutations was 11%.

In one 71 year old patient with anaplastic thyroid cancer, *ALK* overexpression was seen [17]. Further analysis demonstrated the presence of a rearrangement and the patient was treated with the *ALK*-inhibitor crizotinib. This resulted in a dramatic response and reduction of the lung metastases by 90%.

Other abnormalities have been reported and sporadically targeted in anaplastic thyroid cancer. These include *braf* which is found in 14-25% of anaplastic thyroid cancer [18, 19].

This has also been associated with dramatic responses to targeted therapy in one case report. These anecdotal results remain to be confirmed in larger studies.

Other mutations commonly found in ATC include PI3KCA (24%), PTEN (16%), RAS (60%) and TP53 (48%) [20].

Molecular testing is commonly performed in anaplastic thyroid cancer using commercial tests such as FoundationOne and Caris. In cases where these results are available, they will be collected to determine if there is any correlation between mutations and responses.

1.1.5.1 Concept

The goal of this multi-center, open-label trial is to measure the impact of treating metastatic anaplastic thyroid cancer patients with immune checkpoint therapy. This trial will potentially lead to the development of new therapy for anaplastic thyroid cancer. The drug to be administered, pembrolizumab is FDA approved with known side effects and is active in many tumor types.

PD-1/PD-L1 expression will be measured and reported for patients undergoing therapy with pembrolizumab. This will help determine if there PD-1 or PD-L1 are predictive biomarkers for anti-PD-1 therapy. It will also add to the data regarding their frequency in aggressive thyroid cancer. Where available, genomic profiling data will be analyzed to determine if there is a correlation between response and mutational status.

1.2 Study Agent(s) Background and Associated Known Toxicities

Refer to the Investigator's Brochure (IB)/approved labeling for detailed background information on pembrolizumab (MK-3475).

1.2.1 Pharmaceutical and Therapeutic Background

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

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an Ig superfamily member related to CD28 and CTLA-4 which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2). The structure of murine PD-1 has been resolved. PD-1 and family members are type I transmembrane glycoproteins containing an Ig Variable-type (V-type) domain responsible for ligand binding and a cytoplasmic tail which is responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM). Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3ζ, PKCθ and ZAP70 which are involved in the CD3 T-cell signaling cascade. The mechanism by which PD-1 down modulates T-cell responses is similar to, but distinct from that of CTLA-4 as both molecules regulate an overlapping set of signaling proteins. PD-1 was shown to be expressed on activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B-cells, T regs and

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

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

1.2.2 Preclinical and Clinical Trial Data

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

1.3 Rationale

1.3.1 Rationale for the Trial and Selected Subject Population

Currently the therapeutic options for metastatic or locally advanced anaplastic thyroid cancer are non-existent. Though many drugs are given in hope of benefitting patients, none have been proven to do so. There are no treatment options that prolong survival, and as a result new agents are desperately needed.

The identification of immune checkpoint inhibitors has transformed the treatment landscape in many different cancers. Where previously there were no good treatment options such as melanoma, immune therapy has dramatically altered the outcomes for patients [21].

A similar change in outcomes is needed in anaplastic thyroid cancer. The relatively broad range of tumor types in which pembrolizumab has shown benefit (breast [22], lymphoma [23], urothelial cancer [24], head and neck cancer [25] as well as others) suggests that aggressive thyroid cancer may also be sensitive to this therapy. The prevalence of PD-L1 overexpression in anaplastic thyroid cancer suggests that for a subset of patients, there may be a dramatic improvement in outcomes. However the paucity of viable alternative treatments means that even modest improvements in PD-L1 low cancers may still have a meaningful impact on patients' lives.

The currently available data does not justify a large randomized study evaluating the impact of pembrolizumab in anaplastic thyroid cancer. If a promising signal of pembrolizumab activity is identified after this initial study; a larger trial is planned to

confirm the results and accurately describe the true impact of pembrolizumab in this disease.

1.4 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 MK-3475. The dose escalation portion of this trial evaluated three dose levels, 1 mg/kg, 3 mg/kg, and 10 mg/kg, administered every 2 weeks (Q2W) in subjects with advanced solid tumors. All three dose levels were well tolerated and no dose-limiting toxicities were observed. This first in human study of MK-3475 showed evidence of target engagement and objective evidence of tumor size reduction at all dose levels (1 mg/kg, 3 mg/kg and 10 mg/kg Q2W). No MTD has been identified to date. 10.0 mg/kg Q2W, 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 MK-3475 program has shown that a lower dose of MK-3475 and a less frequent schedule may be sufficient for target engagement and clinical activity.

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

A population pharmacokinetic analysis has been performed using serum concentration time data from 476 patients. Within the resulting population PK model, clearance and volume parameters of MK-3475 were found to be dependent on body weight. The relationship between clearance and body weight, with an allometric exponent of 0.59, is within the range observed for other antibodies and would support both body weight normalized dosing or a fixed dose across all body weights. MK-3475 has been found to have a wide therapeutic range based on the melanoma indication. The differences in exposure for a 200 mg fixed dose regimen relative to a 2 mg/kg Q3W body weight based regimen are anticipated to remain well within the established exposure margins of 0.5 – 5.0 for MK-3475 in the melanoma indication. The exposure margins are based on the notion of similar efficacy and safety in melanoma at 10 mg/kg Q3W vs. the 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, 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.

1.5 Correlative Studies

The diagnosis of anaplastic thyroid cancer is often delayed due to it being a rare diagnosis and one without clear pathognomonic pathologic findings. Tissue from patients who are enrolled on to this study will be reviewed at UT Southwestern medical center pathology by a pathologic specialized in endocrine neoplasia. Central review and confirmation of the diagnosis will not be a prerequisite for study eligibility.

Additionally tissue will be tested for PD-L1 expression, as well as other potential biomarkers predictive of disease response to the study agent. In studies in squamous lung cancer, high PD-L1 expression was associated with an enhanced improved outcomes with pembrolizumab therapy[13].

2.0 STUDY OBJECTIVES

2.1 Primary Objectives

2.1.1 To determine the response rate of pembrolizumab when administered at 200 mg IV every 3 weeks in patients with anaplastic thyroid cancer.

2.2 Secondary Objectives

2.2.1 To describe the median progression free survival in anaplastic thyroid cancer patients treated with pembrolizumab compared to previously published values.

2.2.2 To describe the median overall survival in anaplastic thyroid cancer patients treated with pembrolizumab compared to previously published values.

2.2.3 To describe the adverse events associated with pembrolizumab when administered at a dose of 200 mg IV every 3 weeks.

2.3 Exploratory/biomarker Objectives

Collection of genomic profiling and PD-L1 status as well as others

2.4 Endpoints

2.4.1 **Primary endpoint:** Best radiographic response of patients who receive pembrolizumab. RECIST 1.1 will be used to describe whether patients demonstrate a complete response, partial response, stable disease or progressive disease. Response rate will be the percentage of patients showing complete or partial response.

2.4.2 **(2.2.1) Secondary endpoint:** Median time from initiation of pembrolizumab until disease progression by RECIST1.1, unacceptable toxicity, withdrawal of consent, or discontinuation from the trial for any other reason.

2.4.3 **(2.2.2) Secondary endpoint:** Time from initiation of pembrolizumab until death.

2.4.4 **(2.2.3) Secondary endpoint:** toxicity and adverse events (CTCAE v.4)

3.0 Subject ELIGIBILITY

Eligibility waivers are not permitted. Subjects must meet all of the inclusion and exclusion criteria to be registered to the study. Study treatment may not begin until a subject is registered.

3.1 Inclusion Criteria

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

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

2. Histologically or cytologically confirmed diagnosis of anaplastic thyroid cancer or undifferentiated thyroid cancer. A diagnosis of possible ATC/UTC will be allowed if the clinical presentation is consistent with anaplastic or undifferentiated thyroid cancer.

3. Patients will be eligible if they meet either criteria:
   a. Unresectable anaplastic thyroid cancer limited to the neck: Patients must have received radiation therapy or surgery to primary tumor and have subsequent evidence of ATC.

   b. Metastatic anaplastic thyroid cancer: either with entirely surgically removed cancer/metastatic only disease, or with disease in the neck not requiring radiation or surgery to the neck mass.

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

5. Have measurable disease based on RECIST 1.1.

6. Patients with a bulky thyroid/neck mass and those in whom airway obstruction is suspected should undergo an evaluation via indirect or direct laryngoscopy to ensure patency of the trachea/airway prior to enrollment

7. Have a performance status of 0-1 on the ECOG Performance Scale.

8. Demonstrate adequate organ function as defined in Table 1, all screening labs should be performed within 14 days of treatment initiation.

Table 1: Adequate Organ Function Laboratory Values

System	Laboratory Value
HEMATOLOGICAL	
Absolute neutrophil count (ANC)	≥1,500 /mcL
Platelets	≥75,000 / mcL
Hemoglobin	≥8 g/dL without transfusion or EPO dependency (within 7 days of assessment)
RENAL	
Serum creatinine **OR** Measured or calculated[a] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 X upper limit of normal (ULN) **OR** ≥60 mL/min for subject with creatinine levels > 1.5 X institutional ULN
HEPATIC	
Serum total bilirubin	≤ 1.5 X ULN **OR**

	Direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 X ULN **OR** **≤** 5 X ULN for subjects with liver metastases
Albumin	≥2.5 mg/dL
COAGULATION	
International Normalized Ratio (INR) or Prothrombin Time (PT) Activated Partial Thromboplastin Time (aPTT)	≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants ≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
[a]Creatinine clearance should be calculated per institutional standard.	

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.

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

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

3.2 Exclusion Criteria

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

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

2. Patients who have received radiation therapy within 7 days prior to the first dose of treatment should be excluded. Treatment-related adverse events must have resolved prior to study treatment.

3. 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.

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

5. Hypersensitivity to pembrolizumab or any of its excipients.

6. 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 acute, non- hematological adverse events due to agents administered more than 4 weeks earlier unless otherwise approved by the Principal Investigator.

- Note: Subjects with ≤ Grade 2 neuropathy, any grade dysphagia, ≤ Grade 2 pain, ≤ Grade 2 weight loss, any grade hyperpigmentation of skin, any grade fatigue, any grade xerostomia, and any grade dysgeusia, are an exception to this criterion and may qualify for the study. Also please note that the presence of a feeding tube to aid with nutrition does not disqualify patients from 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.

Has had prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to the first protocol treatment or who has not recovered (i.e., ≤ Grade 1 or at baseline) from acute, non-hematological adverse events due to a previously administered agent unless otherwise approved by the Principal Investigator.

- Note: Subjects with ≤ Grade 2 neuropathy, any grade dysphagia, ≤ Grade 2 pain, ≤ Grade 2 weight loss, any grade hyperpigmentation of skin, any grade fatigue, any grade xerostomia, and any grade dysgeusia, are an exception to this criterion and may qualify for the study. Also please note that the presence of a feeding tube to aid with nutrition does not disqualify patients from study.

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

-

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

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

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

10. Has known history of, or any evidence of active, non-infectious pneumonitis.

11. Has an active infection requiring systemic therapy.

12. 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.

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

14. 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.

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

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

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

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

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

4.0 TREATMENT PLAN

4.1 Treatment Dosage and Administration

The treatment to be used in this trial is outlined below in Table 2. This treatment will be administered as an outpatient.

Table 2: Trial Treatment

Trial treatment should begin on the day 1 of cycle.

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

4.1.1 Dose Selection

The rationale for selection of doses to be used in this trial is provided in Section 1.4– Background and Rationale.

4.2 Toxicities and Dosing Delays/Dose Modifications

Any subject who receives treatment on this protocol will be evaluable for toxicity. Each patient will be assessed for the development of toxicity according to the Time and Events table (Table 3). Toxicity will be assessed according to the NCI Common Toxicity Criteria for Adverse Events (CTCAE), version 4.0. Dose adjustments should be made according to the system showing the greatest degree of toxicity.

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 3 below. See Section 5.6.1 and Events of Clinical Interest Guidance Document for supportive care guidelines, including use of corticosteroids.

Table 3: Dose Modification Guidelines for Drug-Related Adverse Events

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Discontinue Subject
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)[1]	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	2-3	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
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	2-4	Therapy with pembrolizumab can be continued while treatment for the thyroid disorder is instituted	Therapy with pembrolizumab can be continued while treatment for the thyroid disorder is instituted.
Infusion Reaction	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[2]	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.

[1] 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.

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

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

4.2.1 Timing of Dose Administration

Trial treatment should be administered on Day 1 of each cycle after all procedures/assessments have been completed as detailed on the Trial Flow Chart (Section

6.0). Trial treatment may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons.

All trial treatments will be administered on an outpatient basis.

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

4.2.2 Trial Blinding/Masking

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

4.3 Concomitant Medications/Treatments

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

4.3.1 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 Duration of Therapy and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the CRF.

All concomitant medications received within 28 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered after 30 days after the last dose of trial treatment should be recorded for SAEs and ECIs as defined in Section 7.2.

4.3.2 Prohibited Concomitant Medications

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

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

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

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

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

a. Rescue Medications & Supportive Care

i. 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 and in greater detail in the ECI guidance document. 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 is instructed to follow the ECI reporting guidance but does not need to follow the treatment guidance (as outlined in the ECI guidance document). Refer to Section 5.2.1 for dose modification.

It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event. Suggested conditional procedures, as appropriate, can be found in the ECI guidance document.

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

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

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

- For **T1DM** or **Grade 3-4** Hyperglycemia
  - Insulin replacement therapy is recommended for Type I diabetes mellitus and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria.
  - Evaluate patients with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.

- **Hypophysitis**:
  - For **Grade 2** events, treat with corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
  - For **Grade 3-4** events, treat with an initial dose of IV corticosteroids followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

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

- **Hepatic**:
  - For **Grade 2** events, monitor liver function tests more frequently until returned to baseline values (consider weekly).
    - Treat with IV or oral corticosteroids
  - For **Grade 3-4** events, treat with intravenous corticosteroids for 24 to 48 hours.
  - When symptoms improve to Grade 1 or less, a steroid taper should be started and continued over no less than 4 weeks.

- **Renal Failure or Nephritis**:
  - For **Grade 2** events, treat with corticosteroids.
  - For **Grade 3-4** events, treat with systemic corticosteroids.
  - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

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

Table 4 below shows treatment guidelines for subjects who experience an infusion reaction associated with administration of pembrolizumab (MK-3475).

Table 4: Infusion Reaction Treatment Guidelines

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

4.4 Diet/Activity/Other Considerations

4.4.1 Diet

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

4.4.2 Contraception

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

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

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

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study they must adhere to the contraception requirement (described above) for the duration of the study and during the follow-up period defined in section 7.2.2-Reporting of Pregnancy and Lactation to the Sponsor and to Merck. If there is any question that a subject will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

4.4.3 Use in Pregnancy

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

The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor. If a male subject impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to the Sponsor and to Merck and followed as described above and in Section 7.2.2.

4.4.4 Use in Nursing Women

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

4.5 Subject Withdrawal/Discontinuation Criteria

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

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

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

Note: For unconfirmed radiographic disease progression,
Note: A subject may be granted an exception to continue on treatment with confirmed radiographic progression if clinically stable or clinically improved.

- Unacceptable adverse experiences as described in Section 5.2.1.2
- Intercurrent illness that prevents further administration of treatment
- Investigator's decision to withdraw the subject
- The subject has a confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements
- The subject is lost to follow-up
- Completed 24 months of uninterrupted treatment with pembrolizumab or 35 administrations of study medication, whichever is later.

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

The End of Treatment and Follow-up visit procedures are listed in Section 6 (Protocol Flow Chart) and Section 7.1.5 (Visit Requirements). After the end of treatment, each subject will be followed for 30 days for adverse event monitoring (serious adverse events will be collected for 90 days after the end of treatment as described in Section 7.2.3.1). Subjects who discontinue for reasons other than progressive disease will have post-treatment follow-up for disease status until disease progression, initiating a non-study cancer treatment, withdrawing consent or becoming lost to follow-up. After documented disease progression each subject will be followed by telephone for overall survival until death, withdrawal of consent, or the end of the study, whichever occurs first.

4.5.1 Discontinuation of Study Therapy after CR

Discontinuation of treatment may be considered for subjects who have attained a confirmed CR that have been treated for at least 24 weeks with pembrolizumab and had at least two treatments with pembrolizumab beyond the date when the initial CR was declared. Subjects who then experience radiographic disease progression may be eligible for up to one year of additional treatment with pembrolizumab via the Second Course Phase at the discretion of the investigator if no cancer treatment was administered since the last dose of pembrolizumab, the subject meets the safety parameters listed in the Inclusion/Exclusion criteria, and the trial is open. Subjects will resume therapy at the same dose and schedule at the time of initial discontinuation.

4.6 Duration of Therapy

In the absence of treatment delays due to adverse events, treatment may continue until:

- Disease progression
- Inter-current illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Subject decides to withdraw from the study, **OR**
- General or specific changes in the patient's condition render the subject unacceptable for further treatment in the judgment of the investigator.

4.7 Duration of Follow Up

Subjects will be followed for 5 years after removal from treatment or until death, whichever occurs first. Subjects removed from treatment for unacceptable adverse events will be followed until resolution or stabilization of the adverse event. Trial follow up will be with clinic visits as indicated, and with a phone call every 3 months if the patient is no longer being seen.

4.8 Removal of Subjects from Protocol Therapy

Subjects will be removed from therapy when any of the criteria listed in Section 5.5 apply. Notify the Principal Investigator, and document the reason for study removal and the date the subject was removed in the Case Report Form. The subject should be followed-up per protocol.

4.9 Subject Replacement

If a patient is enrolled but does not receive pembrolizumab for any reason, they may be replaced with another trial participant. Patients that receive at least one dose of pembrolizumab will not be replaced.

5.0 STUDY PROCEDURES

5.1 Screening/Baseline Procedures

Assessments performed exclusively to determine eligibility for this study will be done only after obtaining informed consent. Assessments performed for clinical indications (not exclusively to determine study eligibility) may be used for baseline values even if the studies were done before informed consent was obtained.

All screening procedures must be performed within 30 days prior to registration unless otherwise stated. The screening procedures include:

5.1.1 Screening assessments to confirm eligibility will be performed as per the schedule of assessments. Documented Informed consent must be obtained before any study specific procedure will be performed.

For treatment on the trial, the patient must have a documented anaplastic/undifferentiated thyroid cancer and meet the remainder of the eligibility criteria. If the diagnosis of ATC/UTC is suspected, patients will be allowed to enroll if they have a compatible clinical picture such as rapidly enlarging thyroid mass. This must be done at the treating center and all study required testing must be completed within the 30 day period prior to day of initiating therapy.

Re-screening of patients will be allowed, if all entry criteria are met during the re-screening phase time period (-30 days to -1 day).

5.1.2 Medical history

Complete medical and surgical history, history of infections, autoimmune disease.

5.1.3 Demographics

Data to be collected on patient characteristics at screening include:

- Demography (including: date of birth, age, patient initials, gender, childbearing potential, race and ethnicity, or as allowed by local regulations)

- ATC diagnosis and extent of disease, including:
  - Date of diagnosis
  - Site of active disease

- Prior antineoplastic therapies (medications, radiation, surgeries)
- Prior and Concomitant Medications, surgical and medical procedures

All other medications taken within 30 days before the first dose of pembrolizumab treatment is administered will be noted in the clinical trial medication record and updated on a continual basis if there is new change to the medication.

5.1.4 Review subject eligibility criteria

According to section 3.

5.1.5 Review previous and concomitant medications

5.1.6 Physical exam including vital signs, height and weight

Vital signs (temperature, pulse, respirations, blood pressure), height, weight

5.1.7 *Performance status*

Performance status evaluated prior to study entry

5.1.8 *Adverse event assessment*

Baseline adverse events will be assessed. See section 7.1 for Adverse Event monitoring and reporting.

5.1.9 *Hematology*

Hgb, platelets, white blood cells (WBC), red blood cells (RBC), differential (basophils, eosinophils, lymphocytes, monocytes, neutrophils (% or absolute))

5.1.10 *Serum chemistries*

Albumin, ALT, AST, calcium, creatinine, total bilirubin, direct bilirubin (only if total bilirubin is ≥ grade 2), blood urea nitrogen (BUN) or urea, magnesium, potassium, sodium, alkaline phosphatase, TSH, T3, Free T4, Creatinine clearance will be calculated using the serum creatinine value.

5.1.11 *Urinalysis*

Macroscopic panel (dipstick) (color, total bilirubin, blood, glucose, ketones, leukocyte esterase, nitrite, pH, protein, specific gravity, urobilinogen)

Microscopic panel (RBC, WBC, casts, crystals, bacteria, epithelial cells)

5.1.12 *ECG*

A standard 12 lead ECG should be used for assessments as clinically indicated.

5.1.13 *Pregnancy test (for females of child bearing potential)*

At screening visit, serum pregnancy test will be performed. Following the screening assessment, urine pregnancy tests should be performed.

5.1.14 *Tumor assessment*

To be performed using radiographic imaging according to section 5.3.1.

5.2 Time and Events Table

Table 5-1 lists the protocol schedule and assessments and indicates when particular assessments will be performed with an “X”. The cycle length is fixed at 21 days, and will be maintained regardless of whether there were dose modifications or interruptions in therapy. If

treatment with pembrolizumab is interrupted, future visits and assessments will continue as listed from cycle 1 day as Day#1 for the purpose of scheduling.

There will be variation of up to +/-3 days allowed in visits and assessment from Cycle 2 onwards.

Table 5-1 Visit evaluation Schedule		**Protocol Section**	**Screening / Baseline**	**Day 1 of Cycle 1 (21d) +/-3**	**Day 1 of Cycle 2 (21d) +/-3**	**Day 1 of Subsequent cycles (21d) +/-3**	**End of study treatment (EoT) (at last visit, or up to 30 days from last dose)**
Visit Number			**1**	**2**	**3**	**4, 5..**	**Last**
Day of cycle			**-30 to -1**	**1**	**D29**	**D57, D85..**	**Last**
Obtain Informed Consent		ICF	X				
Patient history							
Inclusion/exclusion criteria		3.2 & 3.3	X				
Documentation of diagnosis of anaplastic thyroid cancer, undifferentiated thyroid cancer, or compatible pathologic appearance and clinical presentation		5.1.1.1.1	X				
Diagnosis and extent of cancer		5.1.1.2	X				
Demography		5.1.1.2	X				
Relevant medical history/current medical conditions		5.1.1.2	X				
Prior antineoplastic therapy (meds, surgery, radiation)		5.1.1.2	X				
Prior/concomitant medications		4.4	X	Continuous			
Surgical and Medical Procedures		4.4	X	Continuous			
Eligibility Screening		5.1.1.1	X				
End of Phase Disposition		5.1.1. 1 and 5.1.3	X Screening Phase Disposition				X End of Treatment Phase
Physical examination		**5.2.2.1**	**X**		**X**	**X**	**X**
Performance status (WHO)		5.2.2.4	X	X	X	X	X
Height		5.2.2.3	X				
Weight		5.2.2.3	X	X	X	X	X
Vital signs		5.2.2.2	X	X	X	X	X

Table 5-1. Visit evaluation Schedule (continued)		**Protocol Section**	**Screening / Baseline**	**Day 1 of Cycle 1 (21d) +/- 3**	**Day 1 of Cycle 2 (21d) +/- 3**	**Day 1 of Subsequent cycles (21d) +/- 3**	**End of study treatment (EoT) (at last visit, or up to 30 days from last dose)**
Visit Number			**1**	**2**	**3**	**4, 5,…**	**Last**
Day of cycle			**-30 to-1**	**1**	**D29**	**D57, D85..**	**Last**
Lab assessments*			X	X	X	X	X
CBC		5.2.2.5.1	X	X	X	X	X
Chemistry, *T3, *T4, *TSH * *Results not required prior to Pembrolizumab infusion*.		5.2.2.5.2	X	X	X	X	X
Creatinine clearance		5.2.2.5.2	X				
Urinalysis (dipstick) with microscopic analysis(*Repeat anytime during study if clinically indicated*)		5.2.2.5.4	X				
Pregnancy test *WOCBP		5.2.2.5.5	X(Serum)		X(Urine)	X(Urine)	X(Urine)
Imaging							
Standard of care imaging of neck/chest/abdomen (CT, MRI) as indicated to areas of known/ suspected disease		5.2.1	X			X (within 0-7d prior to every even cycle)	
Standard of Care Imaging of the brain at baseline and then as clinically indicated (MRI/CT)		5.2.1	X			X (if known or suspected brain metastases)	
Safety							
Adverse events		7.1	X	Continuous			
Drug administration		**4.1**		X	X	X	

5.3 Trial Procedures

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

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

5.3.1 Screening/Baseline

Screening assessments to confirm eligibility will be performed as per the schedule of assessments. Documented Informed consent must be obtained before any study specific procedure will be performed. After meeting all the eligibility criteria, patients must sign a consent form for therapeutic portion of the trial.

For the therapeutic portion of the trial, the patient must meet the remainder of the eligibility criteria. This must be done at the treating center and all study required testing must be completed within the 30 day period prior to day of initiating therapy.

Re-screening of patients will be allowed, if all entry criteria are met during the re-screening phase time period (-30 days to -1 day).

5.3.2 Administrative Procedures

5.3.2.1 Informed Consent

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

5.3.3 General Informed Consent

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

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

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

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

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

5.3.3.1 Inclusion/Exclusion Criteria

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

5.3.3.2 Medical History

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

5.3.3.3 Patient demographics and other baseline characteristics

Data to be collected on patient characteristics at screening include:

-Demography (including: date of birth, age, patient initials, gender, childbearing potential, race and ethnicity, or as allowed by local regulations)

-Relevant medical history

-ATC diagnosis and extent of disease, including:
- Date of diagnosis
- Site of active disease
- Prior antineoplastic therapies (medications, radiation, surgeries)
- Prior and Concomitant Medications, surgical and medical procedures

All other medications taken within 30 days before the first dose of pembrolizumab treatment is administered will be noted in the clinical trial medication record and updated on a continual basis if there is new change to the medication.

5.3.3.4 Information to be collected on screening failures

A patient who signs an informed consent but fails to satisfy all eligibility criteria for any reason will be considered a screen failure. The reason for not entering the treatment protocol will be entered on the Screening Phase Disposition Page. The demographic information, informed consent, and Inclusion/Exclusion pages will be completed for Screen Failure patients. No other data will be entered into the clinical database for patients who are screen failures, unless the patient experienced a Serious Adverse Event during the Screening Phase (see Section 7 for SAE reporting details).

Subjects who signed ICF but are considered ineligible after signing the study consent will be considered as screening failures, and data will be handled in the same manner.

The following information will be recorded for screening failure patients:

- Screening Phase Disposition page (including reason for not satisfying eligibility criteria and being started on treatment).
- Informed consent.
- Demography.
- Adverse Events (only if an SAE occurs).
- Inclusion/Exclusion Criteria.

5.3.4 Treatment period

Following completion of screening procedures and verifying patient eligibility, the patient will be approved for treatment per protocol.

The study treatment phase begins on Cycle 1, Day 1 with the first administration of pembrolizumab and will continue to receive treatment until disease progression by RECIST,

unacceptable toxicity, withdrawal of consent, or discontinuation of the trial for any other reason whichever occurs first. Patients who have RECIST-defined PD as assessed by the investigator but who, in the opinion of the investigator, have evidence of continued clinical benefit from pembrolizumab may continue to receive the study medication upon approval by the principal investigator. In such cases, these patients must continue to be followed for safety and efficacy assessments as per the schedule of assessments. Patients will be assessed as per visit schedule in Table 5-1.

Visit windows of ± 3 days from scheduled study assessments will apply during and beyond Cycle 2.

5.3.4.1 Treatment phase and duration of treatment

Patients eligible for treatment will receive pembrolizumab. The first dose of each cycle will be administered after evaluation at the study center. Patients will remain on study and receive pembrolizumab until there is evidence of disease progression by RECIST, unacceptable toxicity, withdrawal of consent, or discontinuation of the trial for any other reason. Patients who have RECIST-defined PD as assessed by the investigator but who, in the opinion of the investigator, have evidence of continued clinical benefit from pembrolizumab may continue to receive the study medication. In such cases, these patients must continue to be followed for safety and efficacy assessments as per the schedule of assessments.

5.3.5 End of treatment visit including study completion and premature withdrawal

5.3.5.1 End of Phase Disposition

Patients will be evaluated upon discontinuation of the pembrolizumab by a clinic visit. At that time all assessments listed for End Of Treatment will be performed. A note will be entered into the clinical trial record will be completed, giving the date and reason for stopping the study treatment.

At a minimum, all patients who discontinue study treatment, including those who refuse to return for a final visit, will be contacted for safety evaluations during the 30 days following the last dose of treatment.

5.3.5.2 Disease Details and Treatments

5.3.5.2.1 Disease Details

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

5.3.5.2.2 Prior Treatment Details

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

5.3.5.2.3 Subsequent Anti-Cancer Therapy Status

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

5.3.5.3 Criteria for patient withdrawal

Patients may voluntarily withdraw from the study (no further study data to be collected) at any time.

Patient death will be considered as a withdrawal from the study. Patients may also be withdrawn (the physician may decide to remove the patient from any further study activity) if any of the following occur:

- Adverse event(s) (see Section 7.1)
- Disease progression
- Major protocol deviation
- Technical problems
- Physician decision
- Non-compliance with study treatment.
- Death
- Completed

Patients must be withdrawn if any of the following occur:

- Lost to follow-up
- Subject/guardian decision
- Pregnancy (Pregnancy will be followed for outcome)

Patients lost to follow up should be recorded as such in the clinical trial record. For patients who are lost to follow-up, the investigator will record the attempts at "due diligence" by documenting in the source documents steps taken to contact the patient, e.g. dates of telephone calls, registered letters, etc.

5.3.5.4 Replacement policy

If an eligible patient is unable to start therapy with pembrolizumab, they may be replaced with another eligible patient if they have not received any study drug.

Apart from the above, patients will not be replaced on this study.

5.4 Assessment types

5.4.1 Efficacy assessments

Efficacy evaluations will be via revised RECIST 1.1 criteria on imaging performed at the conclusion of every 2 cycles. Target lesions will be identified prior to initiation of therapy on imaging and will be followed on subsequent imaging. Progression must be documented on imaging.

Imaging exams will be according to standard of care guidelines to areas of known/suspected disease. These will include CT of the neck, chest, abdomen and pelvis as well as MRI of the brain. Other tests may be clinically indicated, these will be ordered according to disease and patient specific guidelines. Imaging of the brain will be required at baseline by CT or MRI per standard of care for anaplastic thyroid cancer.

5.4.2 Safety and tolerability assessments

Safety will be monitored by the assessments described below as well as the collection of AEs at every visit. For details on AE collection and reporting, refer to Section 7. Significant findings that were present prior to the signing of informed consent must be included in the relevant medical history/current medical conditions in the clinical trial record. Significant new findings that begin or worsen after informed consent must be recorded in the clinical trial record.

5.4.2.1 Physical examination

Physical examinations will include an examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, and

a basic nervous system evaluation. Information about the physical examination will be present in the source documentation. For the assessment schedule refer to Table 5-1.

Significant findings that were present prior to the signing of informed consent must be included in the clinical trial record. Significant new findings that begin or worsen after informed consent must be recorded in the clinical trial record.

5.4.2.2 Vital signs

Vital signs include body temperature, blood pressure and pulse measurements. Blood pressure (systolic and diastolic) and pulse should be measured.

For the assessment schedule refer to Table 5-1.

5.4.2.3 Height and weight

Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram [kg]) will be measured. Height will be measured at screening only.

For the assessment schedule for weight refer to Table 5-1.

5.4.2.4 Performance status

WHO performance status will be assessed as per the assessment schedule (refer to Table 5-1).

Assessment of WHO performance status (Table 5-2) will be performed within the time windows described above of the scheduled assessment, even if study medication is being held. More frequent examinations may be performed at the investigator's discretion, if medically indicated.

Table 5-2: WHO Performance status scale

Score	Performance Status
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light housework, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

5.4.2.5 Laboratory evaluations

Local site laboratories will be used for the analysis of scheduled hematology, biochemistry, urine, and other blood specimens collected as part of safety monitoring. All unscheduled blood testing will be performed locally, with exceptions for emergency conditions. The time windows granted for laboratory evaluations are identical to the corresponding visit time windows for each visit (refer to Section 5.1).

Laboratory abnormalities that are considered clinically significant, induce clinical signs or symptoms, require concomitant therapy or require changes in pembrolizumab treatment constitute an adverse event (AE) and must be reported as an AE in the clinical trial record. Laboratory values obtained at the screening visit will be used to assess eligibility to meet inclusion criteria. In addition, eligible patients must have baseline laboratory assessments performed on Cycle 1 Day 1 or within 24 hours prior to dosing.

5.3.2.5.1 Hematology
Hematology assessments of the parameters listed in Table 5-3 will be tested as per the schedule of assessments (Table 5-1).

Table 5-3: Local Clinical laboratory parameters collection plan

Test Category	Test Name **Normal ranges based on local laboratory standard of care parameters*
Hematology	Hgb, platelets, white blood cells (WBC), red blood cells (RBC), differential (basophils, eosinophils, lymphocytes, monocytes, neutrophils (% or absolute))
Chemistry	Albumin, ALT, AST, calcium, creatinine, total bilirubin, direct bilirubin (only if total bilirubin is ≥ grade 2), blood urea nitrogen (BUN) or urea, TSH, T3, Free T4, potassium, sodium, alkaline phosphatase,
Creatinine clearance	Creatinine clearance
Urinalysis	Macroscopic panel (dipstick)(color, total bilirubin, blood, glucose, ketones, leukocyte esterase, nitrite, pH, protein, specific gravity, urobilinogen) Microscopic panel (RBC, WBC, casts, crystals, bacteria, epithelial cells)
Pregnancy test	For women of childbearing potential(WOCBP) : At screening visit, serum pregnancy test At subsequent cycles, urinary pregnancy test. If local requirements dictate otherwise, local regulations should be followed

5.4.2.5.1 Hematology
Hematology assessments of the parameters listed in Table 5-3 will be tested as per the schedule of assessments (Table 5-1).

5.4.2.5.2 Clinical chemistry and Creatinine clearance
Clinical chemistry and Creatinine clearance assessments of the parameters listed in Table 5-3 will be tested as per the schedule of assessments (Table 5-1).

5.4.2.5.3 Urinalysis
Dipstick measurements will be performed as per Table 5-3 and according to the schedule of assessments (Table 5-1). Any significant findings on dipstick will be followed up with microscopic evaluation as per Table 5-3. Urinalysis after baseline will be performed only if clinically indicated, it is not mandatory.

5.4.2.5.4 Pregnancy and assessments of fertility
During screening, a serum pregnancy test will be completed. Starting on day 1 of Cycle 2, and at EOT, urinary pregnancy test (dipstick) will be performed. The time windows granted for pregnancy testing are identical to the corresponding visit time windows for each visit. If local requirements dictate otherwise, local regulations should be followed.

Women who are determined not to be of child bearing potential before the study will only be tested at screening. When non-child bearing potential status is determined during the study, further pregnancy testing will not be continued. Women are considered post-menopausal if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms), and otherwise not of child bearing potential if they have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

The time windows granted for pregnancy testing are identical to the corresponding visit time windows for each visit.

If a positive pregnancy test is performed in between study visits, the patients must immediately notify the investigator.

5.4.2.6 Cardiac assessments

5.4.2.6.1 Electrocardiogram (ECG)

A standard 12 lead ECG should be used for assessments. ECG's will be performed as clinically indicated. All ECGs will be performed locally and reviewed by investigator.

Interpretation of the tracing must be made by a qualified physician and documented. Clinically significant abnormalities present when the patient signs the informed consent should be reported. New or worsened clinically significant findings occurring after informed consent must be recorded.

5.4.3 Safety Follow-Up Visit

The mandatory Safety Follow-Up Visit should be conducted approximately 30 days after the last dose of trial treatment or before the initiation of a new anti-cancer treatment, whichever comes first. All AEs that occur prior to the Safety Follow-Up Visit should be recorded. Subjects with an AE of Grade > 1 will be followed until the resolution of the AE to Grade 0-1 or until the beginning of a new anti-neoplastic therapy, whichever occurs first. SAEs that occur within 90 days of the end of treatment or before initiation of a new anti-cancer treatment should also be followed and recorded. Subjects who are eligible for retreatment with pembrolizumab may have up to two safety follow-up visits, one after the Treatment Period and one after the Second Course Phase.

5.4.3.1 Follow-up Visits

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

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

5.4.3.1.1 Survival Follow-up

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

5.4.3.2 Second Course Phase (Retreatment Period)

Subjects who stop pembrolizumab with SD or better may be eligible for up to one year of additional pembrolizumab therapy if they progress after stopping study treatment. This retreatment is termed the Second Course Phase of this study and is only available if the study remains open and the subject meets the following conditions:

- **Either**
  - Stopped initial treatment with pembrolizumab after attaining an investigator-determined confirmed CR according to RECIST 1.1, and
    - Was treated for at least 24 weeks with pembrolizumab before discontinuing therapy
    - Received at least two treatments with pembrolizumab beyond the date when the initial CR was declared

OR

  - Had SD, PR or CR and stopped pembrolizumab treatment after 24 months of study therapy for reasons other than disease progression or intolerability

AND

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

Subjects who restart treatment will be retreated at the same dose and dose interval as when they last received pembrolizumab. Treatment will be administered for up to one additional year.
Visit requirements are outlined in Trial Flow Chart.

6.0 Measurement of Effect

6.1 Antitumor Effect- Solid Tumors

Response and progression will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee [*JNCI* 92(3):205-216, 2000]. Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST v1.1 criteria.

6.1.1 Definitions

Evaluable for toxicity. All subjects will be evaluable for toxicity from the time of their first treatment with study drug.

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

6.1.2 Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm with conventional techniques (CT, MRI, x-ray) or as ≥10 mm with spiral CT scan. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Previously irradiated lesions are non-measurable except in cases of documented progression of the lesion since the completion of radiation therapy.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <20 mm with conventional techniques or <10 mm using spiral CT scan), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all non-measurable.

Target lesions. All measurable lesions up to a maximum of 3 lesions per organ and 6 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) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor response.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 6 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

6.1.3 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 28 days 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 when both methods have been used to assess the antitumor effect of a treatment.

Provide each method and note timeframe for when each will be done (e.g., every 6 weeks, every 2 cycles, etc.). Examples include:

Conventional CT and MRI. These techniques should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen, and pelvis.

CT scans of the neck, chest, abdomen and pelvis will be performed at baseline and every two cycles according to standard of care. Other imaging of these areas such as PET/MRI will be allowed if CT cannot be performed.
MRI of the brain will be performed at baseline and as clinically indicated. Wherever it can be safely given, radiographic contrast agents should be given for the imaging studies.

6.1.4 Response Criteria

6.1.4.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions, determined by two separate observations conducted not less than 4 weeks apart. There can be no appearance of new lesions.

Partial Response (PR): At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD. There can be no appearance of new lesions.

Progressive Disease (PD): At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started, or the appearance of one or more new lesions.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started.

6.1.4.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level.

Incomplete Response/Stable Disease (SD): Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions

6.1.4.3 Evaluation of Best Overall Response

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

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Response for this Category Also Requires:
CR	CR	No	CR	≥4 wks. confirmation
CR	Non-CR/Non-PD	No	PR	≥4 wks. confirmation
PR	Non-PD	No	PR	
SD	Non-PD	No	SD	documented at least once ≥4 wks. from baseline
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD*	Yes or No	PD	
Any	Any	Yes	PD	

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

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

Note: If subjects respond to treatment and are able to have their disease resected, the patient's response will be assessed prior to the surgery.

6.1.5 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 recurrent 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.

6.1.6 Progression-Free Survival

Progression-free survival (PFS) is defined as the duration of time from start of treatment to time of progression.

6.2 Safety/tolerability

Analyses will be performed for all subjects having received at least one dose of study drug. The study will use the CTCAE version 4.0 for reporting of non-hematologic adverse events (http://ctep.cancer.gov/reporting/ctc.html) and modified criteria for hematologic adverse events.

7.0 ADVERSE EVENTS

7.1 Experimental Therapy

For the most recent safety update, please refer to the current Investigator's Brochure or Study Agent Prescribing Information.

7.1.1 Contraindications

Pembrolizumab is approved by the FDA for use in melanoma. In its current labeling, there are no contraindications listed. Based on currently available data, there are no absolute contraindications to its usage in patients.

7.1.2 Special Warnings and Precautions for Use

There are concerns about pembrolizumab side effects, often immune-related. Always refer to the package insert, any immune related toxicity should be carefully evaluated and considered serious. The relevant section from Lexicomp is provided below.

• Gastrointestinal toxicity: Immune-mediated colitis (including microscopic colitis) has occurred, including cases of grade 2 or 3 colitis. The median time to onset of colitis was 6.5 months (range: ~2 to 10 months) and the mediation duration was 2.6 months (range: 4 days to 3.6 months). Grade 2 or 3 colitis was managed with high-dose systemic corticosteroids (prednisone ≥40 mg/day [median initial dose 70 mg/day] or equivalent) with a median duration of initial corticosteroid therapy of 7 days (range: 4 to 41 days), followed by a corticosteroid taper. Patients with colitis experienced complete resolution. May require treatment interruption, systemic corticosteroid therapy, or permanent discontinuation. Monitor for signs and symptoms of colitis; administer systemic corticosteroids for grade 2 or higher colitis.

• Hepatotoxicity: Hepatitis, including autoimmune hepatitis, occurred (case reports, including 1 case of grade 4 hepatitis). The median onset for grade 4 hepatitis was 22 days; the duration was 1.1 months. Grade 4 hepatitis was managed with high-dose systemic corticosteroids (prednisone ≥40 mg/day or equivalent), followed a corticosteroid taper. Monitor for liver function changes. May require treatment interruption, systemic corticosteroids (for grade 2 or higher toxicity), or permanent discontinuation.

• Hypophysitis: Immune-mediated hypophysitis occurred (1 case of grade 2 and one case of grade 4). The time to onset was 1.3 and 1.7 months, respectively. Hypophysitis was managed with high-dose systemic corticosteroids (prednisone ≥40 mg/day or equivalent), followed by a corticosteroid taper. Patients then remained on physiologic corticosteroid replacement. Monitor for signs/symptoms of hypophysitis. May require treatment interruption, systemic corticosteroids (for grade 2 or higher toxicity), or permanent discontinuation.

• Nephrotoxicity: Nephritis, including autoimmune nephritis (1 case) and interstitial nephritis with renal failure (2 cases), has occurred. The onset for autoimmune nephritis was 11.6 months after the first dose and 5 months after the last dose, and duration was 3.2 months. Acute interstitial nephritis was confirmed by renal biopsy in 2 patients with grades 3/4 renal failure. These cases were managed with high-dose systemic corticosteroids (prednisone ≥40 mg/day equivalent, followed by a corticosteroid taper), with full recovery. Monitor for renal function changes. May require treatment interruption, systemic corticosteroids (for grade 2 or higher toxicity), or permanent discontinuation.

• Pulmonary toxicity: Immune-mediated pneumonitis has been observed, including cases which were grade 2 and 3. The median time to development was 5 months (range: ~2 days to ~10 months) and the median duration was ~5 months (range: 1 week to 14.4 months). Some patients required initial management with high-dose systemic corticosteroids (median initial prednisone dose of 63.4 mg/day

or equivalent), the median duration of initial corticosteroid therapy was 3 days (range: 1 to 34 days) followed by a corticosteroid taper. Most patients with grade 2 or 3 pneumonitis had complete resolution. May require treatment interruption, corticosteroid therapy, or permanent discontinuation. Monitor for signs and symptoms of pneumonitis; if pneumonitis is suspected, evaluate with radiographic imaging and administer systemic corticosteroids for grade 2 or higher pneumonitis.

• Thyroid disorders: Immune-mediated hyperthyroidism and hypothyroidism have occurred. The median onset for hyperthyroidism was 1.5 months (range: 2 to 8 weeks), and the median duration was 2.8 months (range: 1 to 6 months). May require management with high-dose systemic corticosteroids (prednisone ≥40 mg/day or equivalent), followed by a corticosteroid taper. Hyperthyroidism resolved in all cases observed in the clinical trial. Hypothyroidism occurred with a median onset of 3.5 months (range: 5 days to 19 months). Hypothyroidism was generally managed with long-term thyroid hormone replacement therapy, although some patients only required short-term replacement therapy. Hypothyroidism did not require systemic corticosteroid therapy or discontinuation. Thyroid disorders may occur at any point in pembrolizumab therapy. Monitor for changes in thyroid function (at baseline, periodically during treatment and as clinically indicated). Administer systemic corticosteroids (for grade 3 or higher hyperthyroidism); may require treatment interruption or permanent discontinuation. Isolated hypothyroidism may be managed with replacement therapy (without corticosteroids and treatment interruption).

• Other immune-mediated toxicities: Other clinically relevant immune-mediated disorders have been observed, including exfoliative dermatitis, uveitis, arthritis, myositis, pancreatitis, hemolytic anemia, partial seizure (in a patient with inflammatory foci in brain parenchyma), and adrenal insufficiency. Myasthenic syndrome, optic neuritis, and rhabdomyolysis have also been observed in patients receiving pembrolizumab. If an immune-mediated adverse event is suspected, evaluate appropriately; withhold treatment and administer systemic corticosteroids based on severity of reaction. Upon resolution to grade 0 or 1, initiate corticosteroid taper (continue tapering over at least 1 month). If reaction remains at grade 1 or less during taper may reinitiate pembrolizumab. Discontinue permanently for severe or grade 3 immune-mediated adverse event that is recurrent or life-threatening.

7.1.3 Interaction with other medications

Refer to the package insert for possible interactions. There are currently no known interactions with other drugs.

7.1.4 Adverse Reactions

7.1.4.1 Adverse Event (AE) Monitoring

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

For subjects receiving treatment with pembrolizumab all AEs of unknown etiology associated with pembrolizumab exposure should be evaluated to determine if it is possibly an event of clinical interest (ECI) of a potentially immunologic etiology (termed immune-related adverse events, or irAEs); see the

separate ECI guidance document in Appendix 4 regarding the identification, evaluation and management of potential irAEs.

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

7.2 Assessing and Recording Adverse Events

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

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

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

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

Adverse events may also occur in screened subjects during any pre-allocation baseline period as a result of a protocol-specified intervention, including washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

Progression of the cancer under study is not considered an adverse event unless it is considered to be drug related by the investigator.

All adverse events will be recorded from the time the consent form is signed through 30 days following cessation of treatment and at each examination on the Adverse Event case report forms/worksheets. A planned hospitalization is not considered reportable; however, if a serious adverse event occurs during the course of the hospitalization, then the event is reportable. The reporting timeframe for adverse events meeting any serious criteria is described in section 7.2.3.1.

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

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

If an adverse event(s) is associated with ("results from") the overdose of a Merck product, the adverse event(s) is reported as a serious adverse event, even if no other seriousness criteria are met. If a dose of Merck's product meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is reported as a non-serious Event of Clinical Interest (ECI), using the terminology "accidental or intentional overdose without adverse effect."

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

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

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

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

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

7.2.3.1 Serious Adverse Events

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

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

Refer to Table 6 for additional details regarding each of the above criteria.

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

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

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

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

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

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

7.3 Adverse Event Monitoring

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

All subjects experiencing an adverse event, regardless of its relationship to study drug, will be monitored until:

- the adverse event resolves or the symptoms or signs that constitute the adverse event return to baseline;
- any abnormal laboratory values have returned to baseline;
- there is a satisfactory explanation other than the study drug for the changes observed; or
- death.

7.3.1 Definition

Adverse Events will be reported as indicated by the appropriate following table (see below).

An adverse event is defined as any untoward or unfavorable medical occurrence in a human research study participant, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, clinical event, or disease, temporarily associated with the subject's participation in the research, whether or not it is considered related to the subject's participation in the research.

Adverse events encompass clinical, physical and psychological harms. Adverse events occur most commonly in the context of biomedical research, although on occasion, they can occur in the context of social and behavioral research. Adverse events may be expected or unexpected.

Severity

Adverse events will be graded by a numerical score according to the defined NCI Common Terminology Criteria for Adverse Events (NCI CTCAE) and version number

specified in the protocol. Adverse events not specifically defined in the NCI CTCAE will be scored on the Adverse Event log according to the general guidelines provided by the NCI CTCAE and as outlined below.

- Grade 1: Mild
- Grade 2: Moderate
- Grade 3: Severe or medically significant but not immediately life threatening
- Grade 4: Life threatening consequences
- Grade 5: Death related to the adverse event

Serious Adverse Events

ICH Guideline E2A and the UTSW IRB define serious adverse events as those events, occurring at any dose, which meets any of the following criteria:

- Results in death
- Immediately life-threatening
- Results in inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Results in a congenital anomaly/birth defect
- Based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

Note: A "Serious adverse event" is by definition an event that meets ***any*** of the above criteria. Serious adverse events may or may not be related to the research project. A serious adverse event determination does not require the event to be related to the research. That is, both events completely unrelated to the condition under study and events that are expected in the context of the condition under study may be serious adverse events, independent of relatedness to the study itself. As examples, a car accident requiring overnight hospitalization would be a serious adverse event for any research participant; likewise, in a study investigating end-stage cancer care, any hospitalization or death would be a serious adverse event, even if the event observed is a primary clinical endpoint of the study. Refer to the UTSW IRB website at http://www.utsouthwestern.net/intranet/research/research-administration/irb/study-management/adverse-events.html to determine when a serious adverse event requires reporting to the IRB.

7.3.2 Unanticipated Problems:

The term "unanticipated problem" is found, but not defined in the regulations for the Protection of Human Subjects at 45 CFR 46, and the FDA regulations at 21 CFR 56. Guidance from the regulatory agencies considers unanticipated problems to include any incident, experience, or outcome that meets ***each*** of the following criteria:

- Unexpected (in terms of nature, severity or frequency) ***AND***
- Definitely, probably, or possibly related to participation in the research ***AND***
- Serious or a possible unexpected problem in that the research places subjects or others at greater risk of harm than was previously known or recognized. Note: Any serious adverse event would always suggest a greater risk of harm.

Follow-up

All adverse events will be followed up according to good medical practices.

7.3.3 Reporting

7.3.3.1 Local unanticipated problems require expedited reporting, and are submitted to the UTSW IRB through the UTSW eIRB and to the SCC DSMC Coordinator. Hardcopies or electronic versions of the eIRB report; FDA Form #3500A forms, or other sponsor forms, if applicable; and/or any other supporting documentation available should be forwarded to the DSMC Coordinator. The DSMC Coordinator forwards the information onto the DSMC Chairman who determines if immediate action is required. Follow-up eIRB reports, and all subsequent SAE documentation that is available are also submitted to the DSMC Chair who determines if further action is required. *(See Appendix IV of the SCC DSMC Plan for a template Serious Adverse Event Form which may be utilized when a sponsor form is unavailable and SAE submission to the eIRB in not required).*

All local serious adverse events which occur on research subjects on protocols for which the SCC is the DSMC of record require reporting to the DSMC regardless of whether IRB reporting is required. Hardcopies or electronic versions of the FDA Form #3500A forms, or other sponsor forms, if applicable; and/or any other supporting documentation available should be forwarded to the DSMC Coordinator.

If the event occurs on a multi-institutional clinical trial coordinated by the Cancer Center, the DOT Manager or lead coordinator ensures that all participating sites are notified of the event and resulting action, according to FDA guidance for expedited reporting. DSMC Chairperson reviews all serious adverse events within upon receipt from the DSMC Coordinator. The DSMC Chairperson determines whether action is required and either takes action immediately, convenes a special DSMC session (physical or electronic), or defers the action until a regularly scheduled DSMC meeting.

Telephone reports to: (Investigator: Saad Khan, office # 214- 648- 4180, pager 972- 229- 4270) UTSW SCC Data Safety Monitoring Committee Coordinator (if fax report is not available) within 1 working day to 214-648-7097.
Written reports to: (Investigator: Saad Khan, office fax # 214 648-1955, 5323 Harry Hines Blvd, Dallas, TX 75390-8852) UTSW SCC Data Safety Monitoring Committee Coordinator Email: SCCDSMC@utsouthwestern.edu Fax: 214-648-5949 or deliver to BLB.306 UTSW Institutional Review Board (IRB) Submit via eIRB with a copy of the final sponsor report as attached supporting documentation

1. SAEs

Local serious adverse events (SAEs) for studies where SCC DSMC is the DSMC of record require reporting to the DSMC coordinator within 2 working days of PI awareness, or as described in the protocol.

2. Unanticipated Problems

Local unanticipated problems require reporting to the UTSW IRB within 2 working days of PI awareness of the event.

Unanticipated problems, including those that occur as non-local events, require reporting to the UTSW IRB within 10 working days of PI awareness of the event.

For further guidance for Investigators regarding safety reporting requirements for INDs and BA/BE studies, refer to FDA Draft Guidance document: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM227351.pdf

7.4 Steps to Determine If an Adverse Event Requires Expedited Reporting

Step 1: Identify the type of adverse event using the NCI Common Terminology Criteria for Adverse Events (CTCAE v4).

Step 2: Grade the adverse event using the NCI CTCAE v4.

Step 3: Determine whether the adverse event is related to the protocol therapy Attribution categories are as follows:

- Definite – The AE *is clearly related* to the study treatment.
- Probable – The AE *is likely related* to the study treatment.
- Possible – The AE *may be related* to the study treatment.
- Unrelated – The AE *is clearly NOT related* to the study treatment.

Note: This includes all events that occur within 30 days of the last dose of protocol treatment. Any event that occurs more than 30 days after the last dose of treatment and is attributed (possibly, probably, or definitely) to the agent(s) must also be reported accordingly.

Step 4: Determine the prior experience of the adverse event.
Expected events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered unexpected, for expedited reporting purposes only, when either the type of event or the severity of the event is not listed in:

- the current known adverse events listed in the Agent Information Section of this protocol;
- the drug package insert;
- the current Investigator's Brochure

7.4.1.1 Events of Clinical Interest

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

1. an overdose of Merck product, as defined in Section 7.2.1 - Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor, that is not associated with clinical symptoms or abnormal laboratory results.
2. an elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

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

evaluation for an underlying etiology. The trial site guidance for assessment and follow up of these criteria can be found in the Investigator Trial File Binder (or equivalent).

1. Additional adverse events:

   A separate guidance document has been provided entitled “Event of Clinical Interest Guidance Document” (previously entitled, “Event of Clinical Interest and Immune-Related Adverse Event Guidance Document”). This document can be found in Appendix 4 and provides guidance regarding identification, evaluation and management of ECIs and irAEs.
   ECIs (both non-serious and serious adverse events) identified in this guidance document from the date of first dose through 90 days following cessation of treatment, or 30 days after the initiation of a new anticancer therapy, whichever is earlier, need to be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220), regardless of attribution to study treatment, consistent with standard SAE reporting guidelines.

   Subjects should be assessed for possible ECIs prior to each dose. Lab results should be evaluated and subjects should be asked for signs and symptoms suggestive of an immune-related event. Subjects who develop an ECI thought to be immune-related should have additional testing to rule out other etiologic causes. If lab results or symptoms indicate a possible immune-related ECI, then additional testing should be performed to rule out other etiologic causes. If no other cause is found, then it is assumed to be immune-related.

7.4.2 Evaluating Adverse Events

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

Table 6: Evaluating Adverse Events

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

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

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

8.0 DRUG INFORMATION

8.1 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

8.1.1 Agent Pembrolizumab

- Other names for the drug: Keytruda, MK-3475
- Classification - type of agent: monoclonal antibody
- Mode of action: monoclonal antibody to PD-1
- Storage and stability: Store vials under refrigeration at 2°C to 8°C (36°F to 46°F).
- Protocol dose: 200 mg every 3 weeks
- Route of administration for this study: intravenous
- Incompatibilities: none
- Availability: provided by Merck free of charge to patients on this study.
- Side effects: Please refer to the pembrolizumab package insert for a comprehensive list of adverse events.

  Common side effects include peripheral edema, fatigue, pruritus, hypoglycemia, elevated AST, cough, arthralgia, diarrhea. Some potentially serious side effects include hypothyroidism, sepsis, pneumonitis, colitis.

- Nursing implications: none

8.1.2 Return and Retention of Study Drug

The study drug pembrolizumab will be destroyed by the UT Southwestern designated investigational drug service pharmacy in accordance with institutional protocols. No patient returned drug will be re-assigned to other patients or diverted to another person.

8.1.2 Study Drug compliance

Drug will be administered by intravenous infusion, with full documentation of administration in the medical record and study records.

8.2 Investigational Product

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of investigational product in accordance with the protocol and any applicable laws and regulations. Clinical Supplies will be provided by Merck as summarized in Table 7.

Table 7 Product Descriptions

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

8.3 Packaging and Labeling Information

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

8.4 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.

8.5 Storage and Handling Requirements

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

8.6 Returns and Reconciliation

The investigator is responsible for keeping accurate records of the clinical supplies received from Merck or designee, the amount dispensed to and returned by the subjects and the amount remaining at the conclusion of the trial.
Upon completion or termination of the study, all unused and/or partially used investigational product will be destroyed at the site per institutional policy. It is the Investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

9.0 STATISTICAL CONSIDERATIONS

9.1 Study Design/Study Endpoints

It is an open-label, multi-institution trial designed to evaluate the activity of pembrolizumab therapy in anaplastic thyroid cancer in patients with no curative alternative therapy. The primary endpoint is the overall response rate of patients with unresectable or metastatic anaplastic thyroid cancer. The secondary endpoint is the progression free survival, overall survival, safety and toxicity of patients with unresectable or metastatic anaplastic thyroid cancer. The exploratory objective is to determine whether any tissue biomarkers or mutations noted on Next Generation Sequencing with FoundationOne Panel correlate for enhanced or impaired response to pembrolizumab therapy, in patients with unresectable or metastatic anaplastic thyroid cancer.

9.2 Sample Size and Accrual

9.2.1 Using the exact binomial test, a sample size of 21 patients would provide 80% power to detect a difference in the response rate from 5% for historical control to a target rate of 25%, with a one-sided significant level of 0.05. The sample size is calculated using PASS 13 software.

9.3 Definition of end of the Study

The arm will be completed when 21 patients have evidence of disease progression by RECIST, unacceptable toxicity, withdrawal of consent, or discontinuation of the trial for any other reason. Patients who have RECIST-defined PD as assessed by the investigator but who, in the opinion of the investigator, have evidence of continued clinical benefit from pembrolizumab may continue to receive the study medication. In such cases, these patients must continue to be followed for safety and efficacy assessments as per the schedule of assessments.

At the completion or discontinuation of study medication, all patients will be seen within 30 days for an end of therapy evaluation. This will include a safety assessment for AE's SAE's. Any unused medication will be returned.

9.4 Early Termination

Treatment on protocol may be terminated early if the Principal investigator or institution assess that the safety of the enrolled subjects will be compromised by continuation of the trial. The procedure followed will be that of the premature withdrawal patient and any patients on treatment will be seen as soon as possible.

9.5 Data confidentiality

Information about protocol subjects will be kept confidential and managed under the applicable laws and regulations. Those regulations require a signed subject authorization informing the subject of the following:

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

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect follow-up safety information (e.g. has the subject experienced any new or worsened AEs) at the end of their scheduled protocol treatment period.

9.6 Statistical methods and data analysis

9.6.1 Full Analysis Set

The Full Analysis Set (FAS) comprises all consented patients.

9.6.2 Safety Set

The Safety Set includes all patients who received at least one dose of pembrolizumab medication.

9.7 Patient demographics/other baseline characteristics

Demographic, disease characteristics and other baseline data will be summarized descriptively for the FAS.

9.8 Treatments (pembrolizumab treatment, concomitant therapies, compliance)

All analyses from this section will be performed on all patients from the safety set. Duration of pembrolizumab treatment exposure will be summarized.

9.9 Data Analyses Plans

The rate of overall response and its 95% confidence interval will be estimated using exact binomial method. Kaplan-Meier methods will be used to estimate the progression free survival and overall survival. Response duration will be summarized for patients who responded. Descriptive summary statistics like median, 25% and 75% percentiles will be used. Toxicities will be dichotomized as none versus any adverse event, or none and mild versus moderate to severe adverse event. Summary tables for adverse events (AEs) will be produced.

10.0 STUDY MANAGEMENT

10.1 Regulatory and ethical compliance

This clinical study was designed, shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC and US Code of Federal Regulations Title 21), and with the ethical principles laid down in the Declaration of Helsinki.

10.2 Informed consent procedures

Eligible patients will only be included on this after providing written (witnessed, where required by law or regulation), IRB/IEC/REB-approved informed consent.

Informed consent must be obtained before conducting any protocol-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the patient source documents. The date when a subject's Informed Consent was actually obtained will be captured in the clinical trial record. The informed consent document will be approved by the IRB.

10.3 Discontinuation of the study

This study will discontinue if terminated by the Institutional Review Board or at the discretion of the Principal Investigator.

10.4 Publication of the study and results

The results of this study will be updated and posted per regulatory requirements, including (but not limited) to databases such as clinicaltrials.gov.

10.4.1 Communication and Publication of Clinical Trial Results

All submitted manuscripts will comply with institutional guidelines and with authorship guidelines of the International Committee of Medical Journal Editors.

10.5 Study documentation, record keeping and retention of documents

The investigator/institution should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial (ICH E6 Section 8) and as required by applicable regulations and/or guidelines. The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

10.6 Confidentiality of study documents and patient records

The investigator must ensure anonymity of the patients; patients must not be identified by names in any trial documents. Signed informed consent forms and patient enrollment log must be kept strictly confidential to enable patient identification.

10.7 Audits and inspections

Source data/documents must be available to inspections by Health Authorities.

10.8 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by the UTSW COI Committee and IRB according to UTSW Policy on Conflicts of Interest. All investigators will follow the University conflict of interest policy.

10.9 Institutional Review Board (IRB) Approval and Consent

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB must approve the consent form and protocol.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the subject will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the subject and the investigator is assured that the subject understands the implications of participating in the study, the subject will be asked to give consent to participate in the study by signing an IRB-approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the subject and by the person who conducted the informed consent discussion.

10.10 Required Documentation

Before the study can be initiated at any site, the following documentation must be provided to the Clinical Research Office.

- A copy of the official IRB approval letter for the protocol and informed consent
- IRB membership list or Federal wide Assurance letter
- CVs and medical licensure for the principal investigator and any associate investigators who will be involved in the study
- Form FDA 1572 appropriately filled out and signed with appropriate documentation (NOTE: this is required if {institution} holds the IND. Otherwise, the affiliate Investigator's signature on the protocol is sufficient to ensure compliance)
- A copy of the IRB-approved consent form
- CAP and CLIA Laboratory certification numbers and institution lab normal values
- Executed clinical research contract

10.11 Registration Procedures

All subjects must be registered with the Clinical Research Office before enrollment to study. Prior to registration, eligibility criteria must be confirmed with the Research Office Study Coordinator. To register a subject, call Pamela Kurian at 214-648-5874 Monday through Friday, 9:00AM-5:00PM.

New subjects will receive a number beginning with 001 upon study consent such that the first subject consented is numbered 001, the second subject consented receives the number 002, etc.

Upon confirmation of eligibility and enrollment as per the afore-mentioned instructions, the subject will maintain the assigned number. For example, subject 001 will remain as subject 001 upon enrollment.

For all sites outside of UTSW, the first patient consented and enrolled at the first site will be subject 01-001. The second subject enrolled at the second site might be 02-003.

Each newly consented subject should be numbered using the schema provided above. Upon registration, the registrar will assign the additional registration/randomization code according to the numbering schema outlined above, which should then be entered as the patient study id in Velos upon updating the status to enrolled.

The numbering schema should clearly identify the site number; the sequential number of the subject enrolled as well as the status of the subjects enrolled so that the number of subjects consented versus the number of subjects actually enrolled may be easily identified.

10.12 Data Management and Monitoring/Auditing

REDCap is the UTSW SCC institutional choice for the electronic data capture of case report forms for this and all SCC Investigator Initiated Trials. REDCap will be used for electronic case report forms in accordance with Simmons Cancer Center requirements.

Other institutions participating in this trial as sub-sites will be expected to enter data into REDCap and upload de-identified source materials when instructed by the Simmons Cancer Center study team to facilitate remote source to case report form verification.

Trial monitoring will be conducted no less than annually and refers to a regular interval review of trial related activity and documentation performed by the DOT, which includes but is not limited to accuracy of case report forms, protocol compliance, timeless and accuracy of Velos entries and AE/SAE management and reporting. Documentation of trial monitoring will be maintained along with other protocol related documents and will be reviewed during internal audit.

Toxicity and dose escalation reviews will be performed through the duration of the trial. These reviews will be documented by the Clinical Research Office and the reports will be distributed to the SCC-DSMC, if needed.

The UTSW Simmons Cancer Center (SCC) Data Safety Monitoring Committee (DSMC) is responsible for monitoring data quality and patient safety for all UTSW SCC clinical trials. As part of that responsibility, the DSMC reviews all local serious adverse events and unanticipated problems in real time as they are reported and reviews adverse events on a quarterly basis. The quality assurance activity for the Clinical Research Office provides for periodic auditing of clinical research documents to ensure data integrity and regulatory compliance. A copy of the DSMC plan is available upon request.

The SCC DSMC meets quarterly and conducts annual comprehensive reviews of ongoing clinical trials, for which it serves as the DSMC of record. The QAC works as

part of the DSMC to conduct regular audits based on the level of risk. Audit findings are reviewed at the next available DSMC meeting. In this way, frequency of DSMC monitoring is dependent upon the level of risk. Risk level is determined by the DSMC Chairman and a number of factors such as the phase of the study; the type of investigational agent, device or intervention being studied; and monitoring required to ensure the safety of study subjects based on the associated risks of the study. Protocol-specific DSMC plans must be consistent with these principles.

10.13 Adherence to the Protocol

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study subject requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

10.13.1 Emergency Modifications

Investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB approval.

For any such emergency modification implemented, an IRB modification form must be completed within five (5) business days of making the change.

10.13.2 Other Protocol Deviations/Violations

All other planned deviations from the protocol must have prior approval by the Principal Investigator and the IRB. According to the IRB, a protocol deviation is any unplanned variance from an IRB approved protocol that:

- Is generally noted or recognized after it occurs
- Has no substantive effect on the risks to research participants
- Has no substantive effect on the scientific integrity of the research plan or the value of the data collected
- Did not result from willful or knowing misconduct on the part of the investigator(s).

An unplanned protocol variance is considered a violation if the variance:

- Has harmed or increased the risk of harm to one or more research participants.
- Has damaged the scientific integrity of the data collected for the study.
- Results from willful or knowing misconduct on the part of the investigator(s).
- Demonstrates serious or continuing noncompliance with federal regulations, State laws, or University policies.

If a deviation or violation occurs without prior approval from the Principal Investigator, please follow the guidelines below:

Protocol Deviations: Personnel will report to any sponsor or data and safety monitoring committee in accordance with their policies. Deviations should be summarized and reported to the IRB at the time of continuing review.

Protocol Violations: Study personnel should report violations within two (2) week of the investigator becoming aware of the event using the same IRB online mechanism used to report Unanticipated Problems.

10.14 Amendments to the Protocol

Should amendments to the protocol be required, the amendments will be originated and documented by the Principal Investigator. A summary of changes document outlining proposed changes as well as rationale for changes, when appropriate, is highly recommended. When an amendment to the protocol substantially alters the study design or the potential risk to the patient, a revised consent form might be required.

The written amendment, and if required the amended consent form, must be sent to the IRB for approval prior to implementation.

10.15 Record Retention

Study documentation includes all Case Report Forms, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government agency regulations and directives require that the study investigator retain all study documentation pertaining to the conduct of a clinical trial. In the case of a study with a drug seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an International Conference on Harmonization (ICH) region. In all other cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

10.16 Obligations of Investigators

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study patients. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected and entered onto the Case Report Forms. Periodically, monitoring visits may be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. At the completion of the study, all case report forms will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

11.0 REFERENCES

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12.0 APPENDICES

12.1 ECOG Performance Status

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

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

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