A Phase II Clinical Trial of Single Agent Pembrolizumab in Subjects with Advanced Adrenocortical Carcinoma

PROTOCOL FACE PAGE FOR MSK THERAPEUTIC/DIAGNOSTIC PROTOCOL

Principal Investigator/Department:	Diane Reidy-Lagunes, MD	Medicine
Co-Principal Investigator(s)/Department:	Leonard Saltz, MD Nitya Raj, MD	Medicine Medicine
Investigator(s)/Department:	Ghassan Abou-Alfa, MD Andrea Cercek, MD Andrew Epstein, MD James Harding, MD David Ilson, MD, PhD Yelena Janjigian, MD David Kelsen, MD Nancy Kemeny, MD Geoffrey Ku, MD Eileen O"Reilly, MD Armin Shahrokni, MD Neil Segal, MD, PhD Zsofia Stadler, MD Anna Varghese, MD Rona Yaeger, MD Kenneth Yu, MD Elizabeth Won, MD Jaclyn Norris, NP Claudia Calderon, NP Michal Segal, RN Danny Khalil, MD Karuna Ganesh, MD Wungki Park, MD Juan Schvartzman, MD Imane El Dika, MD Louise Connell, MD Marinela Capanu, PhD Anuradha Gopalan, MD Seth Katz, MD, PhD Jeremy Durack, MD, MS Ellen Hollywood, NP Erica Kaufmann, NP	Medicine Medicine Medicine Medicine Medicine Medicine Medicine Medicine Medicine Medicine Medicine Medicine Medicine Medicine Medicine Medicine Nursing Nursing Nursing Medicine Medicine Medicine Medicine Medicine Medicine Biostatistics Pathology Radiology Interventional Nursing Nursing
Consenting Professional(s)/Department:	Ghassan Abou-Alfa, MD Andrea Cercek, MD Andrew Epstein, MD James Harding, MD	Medicine Medicine Medicine Medicine Medicine

	David Ilson, MD, PhD	Medicine
	Yelena Janjigian, MD	Medicine
	David Kelsen, MD	Medicine
	Nancy Kemeny, MD	Medicine
	Geoffrey Ku, MD	Medicine
	Eileen O"Reilly, MD	Medicine
	Armin Shahrokni, MD	Medicine
	Diane Reidy-Lagunes, MD	Medicine
	Nitya Raj, MD	Medicine
	Leonard Saltz, MD	Medicine
	Neil Segal, MD, PhD	Medicine
	Zsofia Stadler, MD	Medicine
	Anna Varghese, MD	Medicine
	Rona Yaeger, MD	Medicine
	Kenneth Yu, MD	Medicine
	Elizabeth Won, MD	Medicine
	Wungki Park, MD	Medicine
	Juan Schvartzman, MD	Medicine
	Imane El Dika, MD	Medicine
	Louise Connell, MD	Medicine
		Medicine
	Karuna Ganesh, MD	
	Jaclyn Norris, NP	Nursing
	Claudia Calderon, NP	Nursing
	Danny Khalil, MD	Medicine
	Ellen Hollywood, NP	Nursing
	Erica Kaufmann, NP	Nursing

Please Note: AConsenting Professional must have completed the mandatory Human Subjects Education and Certification Program.

Table of Contents

1.0 PROTOCOL SUMMARY AND/OR SCHEMA

Title of Study: A phase II clinical trial of single agent pembrolizumab in subjects with advanced adrenocortical carcinoma (ACC)
Study Centers: Memorial Sloan Kettering Cancer Center (MSKCC)
Trial Phase: II
Clinical Indication: Adrenocortical carcinoma (ACC)
Trial Type: Interventional
Type of control: No treatment control
Route of administration: Intravenous (IV)
Trial blinding: Unblinded open-label
Groups: Pembrolizumab 200 mg every 3 weeks (Q3W)
Number of trial subjects: 21-39 (21 first stage; up to 39 if promising)
Estimated duration of trial: Approximately 36 months from the time the first subject signs the informed consent until the last subject's last visit.
Study Design: This will be a single center, non-randomized, single arm phase II clinical trial using a Simon two stage minimax design. It will be conducted to determine the efficacy and safety of pembrolizumab in subjects with advanced ACC (which is defined as either unresectable or stage IV metastatic disease).All subjects will receive pembrolizumab via IV infusion at 200 mg Q3W, and continue treatment Q3W for up to 24 months, or until documented disease progression, unacceptable side effects or intercurrent illness that prevents further administration of treatment, investigators" decision to withdraw the subject, subject withdraws consent, pregnancy of the patient, noncompliance of the patient, or for administrative reasons. For subjects who do receive treatment for 24 months in the absence of disease progression, there will be the option to resume treatment for an additional 12 months in the future upon disease progression. Patients will be evaluated by physical exam and routine blood tests every 3 weeks during the study period. CT or MRI will be performed during screening, and then at 9 week intervals. Evaluation of tumor responses will be performed according to RECIST v1.1, however subjects may continue to receive pembrolizumab beyond radiographic progression in the absence of clinical deterioration given the potential for tumor flare with immune modulating therapies, after discussion with the Principal Investigator. After the end of treatment, each subject will be followed for 30 days for adverse event monitoring (serious adverse events and events of clinical interest will be collected for 90 days after the end of treatment or 30 days after the end of treatment if the subject initiates new cancer therapy, whichever is earlier). Subjects who discontinue treatment for reasons other than disease progression will have posttreatment follow-up for disease status until disease progression, initiating a non-study cancer treatment, withdrawing consent, or becoming lost to follow-up. All subjects will be followed by telephone contact for overall survival until death or withdrawal of consent. The primary endpoint of this trial is to determine the anti-tumor activity of pembrolizumab by objective response rate (ORR) using RECIST v1.1 in subjects with unresectable or stage IV ACC. A Simon two stage minimax design will be employed to carry out this objective. In the first stage, 21 patients will be enrolled. If at least 3 out of 21 patients respond (partial response - PR or complete response - CR), we will enroll an additional 18 patients for a total of 39 patients. At the end of the study, 8 of 39 patients will need to respond to consider the therapy promising. The study will be complete when all subjects have either completed 24 months of drug therapy, progressed, or discontinued from the study for other reasons. The accrual time is estimated to be 2 years. Although subjects will be enrolled regardless of PD-L1 status, subjects will be required to provide tissue of a tumor lesion (either archived tissue or a fresh biopsy before initiating therapy) to be evaluated at a central laboratory for expression status of PD-L1 by immunohistochemistry. We anticipate that 10-20% of subjects will have disease that responds to treatment and will be amenable to surgical resection. In patients who have a PR or CR and who have disease amenable to surgical resection,

surgically resected tissue will be collected when available. In patients with tumor response who do not have disease amenable to surgical resection, an optional core biopsy will be requested and performed after obtaining patient consent. All specimens (biopsies and surgical specimens) will undergo complete characterization of the immune milieu; tumor immunohistochemistry may be performed for PD-L1 expression and quantification of tumor infiltrating lymphocyte (TIL) subtypes, including CD8+ T-cells, CD4+ T-cells, Regulatory T-cells (Treg), and Myeloid Derived Suppressor Cells (MDSCs). Peripheral blood samples will be obtained in all patients at baseline then weeks 3, 6 and 9. Plasma may be analyzed for change in antibody responses to a broad panel of antigens (seromics). Flow cytometry may be performed for peripheral blood immune cell phenotype and their activation status, including CD8+ T-cells, CD4+ T-cells, Tregs, and MDSCs. The amount of PD-L1 expression, changes in immune cell repertoire and activation status within the tumor and peripheral blood as well as immune responses against specific tumor antigens will be correlated with clinical outcome in an exploratory manner in order to identify predictive makers for response, and to further our understanding of pembrolizumab in ACC.

2.0 OBJECTIVES AND SCIENTIFIC AIMS

- The primary objective is to determine the anti-tumor activity of pembrolizumab by objective response rate (ORR) (CR and PR) using RECIST v1.1 in subjects with advanced ACC (either unresectable or stage IV ACC).
- The secondary objectives are to:
    - Determine the safety and tolerability of pembrolizumab in subjects with advanced ACC.
    - Evaluate the expression of PD-L1 (B7H1) using immunohistochemical staining on ACC tumor cells.
    - Identify and characterize the populations and activation status of tumor infiltrating lymphocytes.
    - Characterize the expression of immune co-receptors on tumor infiltrating lymphocytes using immunohistochemical staining.
    - Estimate the event free survival (EFS) and overall survival (OS) using RECIST v1.1 in subjects with advanced ACC.
- The exploratory objectives are to investigate both blood and tumor biomarkers for their association with efficacy. In patients where the tumor responds, we will ask them for a post-treatment tissue biopsy to see if we can evaluate a marker to help predict response.

3.0 BACKGROUND AND RATIONALE

3.1 Adrenocortical carcinoma (ACC)

ACCs are rare and aggressive tumors, with an incidence of 0.5-2 per million in the United States with 5-year survival less than 35%.[1] Nearly 60% of patients present with metastatic disease at the time of diagnosis and even after complete surgical resection, recurrences are common. In a single center report of 202 cases of ACC, 40% of patients with stage I to III disease had developed distant metastases two years after diagnosis [2, 3].

Unfortunately treatment options for ACC are limited. Mitotane, an adrenocorticolytic drug, is the only FDA approved drug for ACC and is marked by low efficacy and high treatment toxicity. Currently mitotane, either alone or in combination with other cytotoxic agents, is used in any line of therapy, including the adjuvant setting, for primary therapy of unresectable disease, and for the treatment of disease recurrence.[4]

In the setting of metastatic disease, few studies have been conducted of primary, single agent, mitotane therapy. In the small reports that are available, which date back to the 1960-70s, the median survival was about 6.5 months, similar to the survival expected in untreated patients.[5-9]

In addition, even when mitotane is used in combination with cytotoxic chemotherapy, results are overall poor. The FIRM-ACT trial, the only phase III trial ever done for ACC, compared treatment with mitotane with etoposide, doxorubicin and cisplatin (EDP) or with streptozocin.[10] Median progression free survival was 5 months for the EDP treated group and 2.1 months for the streptozocin treated arm, with median OS of 14.8 versus 12 months, respectively. ≥ Grade 3 toxicity was seen in 58.1% of EDP treated patients and 41.6% of streptozocin treated patients. In an attempt to identify targeted therapy options, despite promising pre-clinical work, targeted therapies for ACC with VEGF inhibitors and IGF-1R monoclonal antibody treatment are marked by early progression and poor overall survival.[11-13]

Given the limited treatment options, there is an urgent need for more effective regimens with less drug toxicity for ACC in order to improve outcomes for these patients. MSKCC has one of the largest ACC programs in the country and we also are building a powerful immunotherapy program under the leadership of Dr. Jedd Wolchok, which will enable us to complete an immunotherapy trial for such a rare disease.

3.2 Rationale for immunotherapy in adrenocortical carcinoma

Immunotherapy represents a promising treatment strategy for ACC despite limited pre-clinical and human data detailing the immune microenvironment. There was initial interest in investigating immunotherapy in ACC after observing a high incidence of endocrine related adverse events leading to adrenal insufficiency as a result of hypophysitis or primary adrenalitis with treatment with ipilimumab.[14] We then looked at publicly available RNA Seq data and noted increased expression of CTLA-4 compared to normal adrenal tissue. RNA Seq data also showed expression of PD-L1, PD-1, B7DC and T cell co-receptors in both normal and cancerous tissue, although this is difficult to interpret and of unknown significance (unpublished data).

Until recently, only one published study by Yamamoto et al., investigated the presence of tumor infiltrating lymphocytes (TILs) in adrenocortical carcinoma.[15] Three patients were studied and TILs were harvested, expanded and stimulated in co-culture and then cytotoxic activity was measured against autologous tumor. In two of the three patients, small but significant cytotoxic activity was present. Unstimulated TILs were unable to mount any type of response, however, in this study staining for immune exhaustion markers such as PD-1 or CTLA-4 were not performed. T cells did express CD45RO, indicative of a memory T cell population. Also of importance, when the researchers examined the T cell receptor repertoire amongst the TILs and compared this to circulating lymphocytes within the blood, they saw a more limited repertoire, which is indicative that these T cells were clonally expanded against a specific tumor antigen.

Characterization of PD-L1 expression on both tumor infiltrating monocytes as well as ACC cell membrane expression was reported earlier this year.[16] Nearly all samples (27/28) from patients with ACC had expression of PD-L1 on tumor infiltrating monocytes and nearly 11% had surface membrane expression on the tumor cells. While the presence of PD-L1 staining described above

is promising, more work in the field of melanoma as well as solid organ tumors have shown that responses to treatment with anti-PD-1 therapy are also seen in patients without staining for PD-L1 either due to tumor heterogeneity or mechanisms yet to be described.

Historically, immunotherapy has focused on treating cancers such as melanoma with a high mutational burden. Adrenocortical carcinoma has marked chromosomal instability but high volume somatic hypermutations are only found in 5% of cases.[17] However, in unpublished data from our institution, metastatic lesions carry a higher mutational rate than those found in their paired primary tumor indicating a rationale for immunotherapy.

Furthermore, recent work, even in melanoma, has found that high mutational burden in itself is not completely predictive of immune response.[18] Work with whole exome sequencing performed in combination with bioinformatics has been able to predict the presence of tumor neoantigens in epithelial based tumors and their likelihood to generate cytotoxic T cell responses.[19] Our institution is currently performing whole exome sequencing of adrenocortical tumors giving us a unique opportunity for secondary endpoint analyses. In addition, steroidogenic proteins expressed by the adrenal gland and adrenocortical carcinomas are known antigenic targets in autoimmune disease in both human and pre-clinical models.[20, 21]

Finally, immunohistochemical diagnosis of ACC is actually made by expression of Melan-A (MART-1), a known antigenic target in melanoma.[22] This has not been studied as a potential antigenic target in ACC, nor has this been investigated in cases of immune mediated endocrine adverse events.

Pembrolizumab is an excellent choice for investigation in ACC, as this agent has already demonstrated activity in solid organ tumors. ACC is an appropriate target for pembrolizumab given the above rationale and the unmet need for novel therapies in this disease, given the lack of currently available treatments.

3.3 Pembrolizumab

3.3.1 Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decade. Accumulating evidence shows a correlation between TILs in cancer tissue and favorable prognosis in various malignancies [23-26]. 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 exploited 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-regulate immune responses as an adaptive mechanism to prevent 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). 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 regulates 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, lymphocytes, monocytes 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.[27] Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor. PD-1 has been suggested to regulate tumor-specific T-cell expansion in subjects with melanoma. This suggests that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and should be considered as an attractive target for therapeutic intervention.

Pembrolizumab (previously known as MK-3475 or SCH 900475) 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.

3.3.2 Preclinical and Clinical Trial Data

3.3.2.1 Non-Clinical Toxicology Summary of Results

In the 1-month and 6-month toxicology study in cynomolgus monkeys, pembrolizumab administered once a week and once every other week respectively, intravenously up to 200 mg/kg resulted in no adverse treatment related effects. The exposure multiple based on a predicted $AUC_{0\text{-}tau}$ of 4464 µg/day/mL at the maximum anticipated human clinical dose of 10 mg/kg Q2W or Q3W is 15-fold at 200 mg/kg, the NOAEL for the 6-month monkey study. Additionally, in the tissue cross-reactivity study of pembrolizumab with human and monkey tissues demonstrated the expected on-target staining of the membranes of mononuclear leukocytes in both species. Off-target cross-reactivity staining was also noted in both species but was limited to cytoplasm of various cell types/tissues and the stroma (extracellular connective tissue matrix), and was considered related to the experimental method artifacts, i.e. tissue processing for IHC, that are well recognized limitations of tissue cross-reactivity studies and, thus not considered toxicologically relevant.

No reproductive or developmental toxicity studies are planned with pembrolizumab. Therefore, inclusion of women of childbearing potential in clinical trials should be in accordance with the study protocol and applicable regulatory guidance (e.g., ICH M3(R2): Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals).

3.3.2.2 Clinical Summary of Results

As of 18-Oct-2013, 1,000 patients have been treated with pembrolizumab at several dose-schedules, including 10 mg/kg every 2 weeks. Pembrolizumab has been generally well tolerated, as expected based on preclinical findings and other anti-PD-1 monoclonal antibodies. As of 18-Oct-2013 no serious infusions reactions have been reported in PN001, however, since the potential exists, investigators should be vigilant to this possibility. Less than 1% of patients thus far assayed had confirmed positive ADA samples and among these, no or no clear impact on exposure has been observed. There is no contraindication to further clinical investigation with pembrolizumab. Pharmacokinetics were as expected, based on pembrolizumab being an IgG mAb and based on preclinical data, which support dosing once every 2 or 3 weeks. Pembrolizumab monotherapy induced an ORR of 25% and 27% in patients with ipilimumab- exposed melanoma by central independent RECIST and oncology review/investigator assessed irRC, respectively. Pembrolizumab monotherapy induced an ORR of 39% and 43% in patients with ipilimumab-naive melanoma by central independent RECIST and oncology review/investigator assessed irRC, respectively. These responses are remarkably durable. The preliminary 1-year survival rate for patients, many of whom have had multiple therapies, including ipilimumab, who receive pembrolizumab is 81%. Pembrolizumab monotherapy induces an ORR of 21% and 24% in patients with previously-treated NSCLC by central independent RECIST/investigator assessed irRC, respectively, with these responses also remarkably durable. Preliminary data suggest higher levels of PD-L1 expression in tumors of NSCLC are associated with increased activity (ORR 67% by investigator assessed irRC/57% by central independent RECIST); additional data are required to define the optimal PD-L1 cut point.

The most commonly reported treatment emergent AEs experienced are fatigue (43.8%), nausea (26.7%), cough (25.3%), pruritus (24.6%), diarrhea (22.3%) and rash (21.5%). Immune-related adverse events were reported in 21.4% of melanoma patients; most of these events (15.8%) were considered drug-related by the investigator. The most commonly reported, immune-related adverse events across the dose-schedules are rash (3.2%), pruritus (2.9%), vitiligo (2.9%), hypothyroidism (2.7%), arthralgia (2.2%), diarrhea (2.2%), and pneumonitis (1.9%). Review of the overall benefit: risk ratio of pembrolizumab favors enrollment of eligible patients into clinical trials of pembrolizumab.

3.3.2.3 Rationale for Dose Selection/Regimen/Modification

An open-label Phase I trial (Protocol 001) was conducted to evaluate the safety and clinical activity of single agent pembrolizumab. The dose escalation portion of that trial evaluated three dose levels, 1 mg/kg, 3 mg/kg, and 10 mg/kg, administered every 2 weeks (Q2W) in subjects with advanced solid tumors. All three dose levels were well tolerated and no dose-limiting toxicities

were observed. This first in human study of pembrolizumab showed evidence of target engagement and objective evidence of tumor size reduction at all dose levels (1 mg/kg, 3 mg/kg and 10 mg/kg Q2W). No MTD was identified. Recent data from other clinical studies within the pembrolizumab program has shown that a lower dose of pembrolizumab and a less frequent schedule may be sufficient for target engagement and clinical activity.

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

A population pharmacokinetic analysis has been performed using serum concentration time data from 476 patients. Within the resulting population PK model, clearance and volume parameters of pembrolizumab were found to be dependent on body weight. The relationship between clearance and body weight, with an allometric exponent of 0.59, is within the range observed for other antibodies and would support both body weight normalized dosing or a fixed dose across all body weights. Pembrolizumab has been found to have a wide therapeutic range based on its use in melanoma.

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.

4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.1 Design

This is a single center, non-randomized, single arm, phase II clinical trial. The primary endpoint of this trial is to assess best overall response rate of pembrolizumab using RECIST v1.1 in subjects with unresectable or stage IV ACC. A Simon minimax 2 stage design will be employed to carry out this objective. In the first stage, 21 patients will be enrolled. If at least 3 out of 21 patients

respond (PR or CR) then we will enroll an additional 18 patients for a total of 39 patients and at the end, at least 8 of 39 patients will need to respond to consider the therapy promising. With 39 patients, we anticipate an improvement from 12% to 29%. The design assumes a type 1 error (falsely accepting a nonpromising drug) and type 2 error (falsely rejecting a promising drug) of 10% each. The probability of early termination is 50%.

4.2 Intervention

All subjects will receive 200 mg of pembrolizumab administered Q3W. Subjects will continue treatment Q3W for up to 24 months, or until documented disease progression, unacceptable side effects or intercurrent illness that prevents further administration of treatment, investigators decision to withdraw the subject, subject withdraws consent, pregnancy of the patient, noncompliance of the patient, or for administrative reasons. For subjects who do receive treatment for 24 months in the absence of disease progression, there will be the option to resume treatment for an additional 12 months upon disease progression in the future. During the study period, patients will be clinically evaluated by physical exam and with routine blood work Q3W. Subjects will be evaluated every 9 weeks with radiographic imaging (CT or MRI) to assess response to treatment by a radiologist using RECIST v1.1. *RECIST will be adapted to accommodate for the tumor response patterns seen with pembrolizumab treatment (e.g., tumor flare), and this adapted RECIST will be used as determined by site assessment for treatment decisions.* Given the possibility of tumor flare, subjects may continue to receive pembrolizumab beyond radiographic disease progression in the absence of clinical deterioration, and after discussion with the Principle Investigator.

Adverse events will be monitored throughout the trial and graded in severity according to the guidelines outlined in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

At the end of treatment, each subject will be followed for 30 days for adverse event monitoring (serious adverse events and events of clinical interest will be collected for 90 days after the end of treatment or 30 days after the end of treatment if the subject initiates new anticancer therapy, whichever is earlier). Subjects who discontinue treatment for reasons other than disease progression will have posttreatment follow-up for disease status until disease progression, initiating a non-study cancer treatment, withdrawing consent, or becoming lost to follow-up. All subjects will be followed by telephone contact for overall survival until death or withdrawal of consent.

Although subjects will be enrolled regardless of PD-L1 status, subjects will be required to provide tissue of a tumor lesion (either archived tissue or a fresh biopsy before initiating therapy) to be evaluated at a central laboratory for expression status of PD-L1 by immunohistochemistry. Exploratory research studies to evaluate the effect of pembrolizumab will be performed in subjects using research blood draws, as well as an optional tumor biopsy in subjects who demonstrate a PR or CR to therapy, in an effort to identify predictive markers for response.

4.3 Estimated Duration of Subject Participation

Subjects may be treated for up to 24 months, and in the absence of disease progression during this time, will have the option in the future to resume treatment for an additional 12 months upon disease progression. All subjects will be followed by telephone contact for OS until death or withdrawal of consent.

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

5.1 Pembrolizumab

Pembrolizumab will be provided by Merck. Pembrolizumab 200 mg will be administered as a 30 minute IV infusion Q3W. Please refer to the Investigator"s Brochure, which contains specific instructions for the preparation of pembrolizumab infusion fluid and administration of the infusion solution.

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 affixed with a clinical label in accordance with regulatory requirements.

6.0 CRITERIA FOR SUBJECT ELIGIBILITY

6.1 Subject Inclusion Criteria

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

1. Be willing and able to provide written informed consent for the trial.
2. Be ≥ 18 years of age on day of signing informed consent.
3. Have histologically- or cytologically- confirmed unresectable or metastatic ACC that is considered incurable by local therapies.
4. Have an ECOG performance status of 0 or 1.
5. Have measurable disease based on RECIST v1.1..
6. Have provided tissue for PD-L1 biomarker analysis from either archived tissue or a newly obtained core or excisional biopsy.
7. Consent for use of archived tissue for research purposes.
8. Demonstrate adequate organ function as defined in Table 1, all screening labs should be performed within 28 days of treatment initiation.

Table 1: Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1,500 /mcL
Platelets	≥100,000 /mcL
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
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 subjects of childbearing potential should have a negative serum pregnancy test within 72 hours prior to receiving 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 9.5.2). Subjects of childbearing potential are those who have not been surgically sterilized or have not been free of 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.

6.2 Subject Exclusion Criteria

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

1. Is currently participating in or has participated in a study of an investigational agent or using an investigational device within 4 weeks prior to the first dose of trial treatment.

2. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment. The use of physiologic doses of corticosteroids for adrenal and pituitary

insufficiency is *not* considered a form of systemic steroid therapy and would not exclude a subject from the study.

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

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

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

5. If subject underwent major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.

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

7. Has known active central nervous system 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 brain metastases for at least 7 days prior to trial treatment. This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability.

8. Has an active autoimmune disease requiring systemic treatment within the past 3 months or a documented history of clinically severe autoimmune disease, or a syndrome that requires systemic steroids or immunosuppressive agents. Subjects with vitiligo or resolved childhood asthma/atopy would be an exception to this rule. Subjects that require intermittent use of bronchodilators or local steroid injections would not be excluded from the study. Subjects with hypothyroidism stable on hormone replacement or Sjorgen"s syndrome will not be excluded from the study. Subjects that have adrenal or pituitary insufficiency that require physiologic corticosteroid replacement therapy would not be excluded from the study.

9. Has evidence of interstitial lung disease or history of (non-infectious) pneumonitis that required steroids or current pneumonitis.

10. Has an active infection requiring systemic therapy.

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

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

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

14. Has received prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways).

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

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

17. Has received a live vaccine within 30 days prior to the first dose of trial treatment.

    - *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.*

7.0 RECRUITMENT PLAN

This study will be available to all patients seen at MSKCC, who meet the eligibility criteria outlined in section 6.0.

Potential research subjects will be identified by doctors from the medical oncology and surgical clinics at MSKCC. The principal investigator, member of the treatment team, or a research study assistant will discuss the study with the patient. They will use the information provided by the patient and/or medical record to confirm that the patient is eligible and to contact the patient regarding study enrollment. All eligible patients, regardless of sex and race, will be approached for participation. The investigators are aware of the NIH policy concerning inclusion of women and minorities in clinical research populations.

Participation in the study is completely voluntary. Patients will be required to read, agree to, and sign an IRB-approved informed consent form prior to registration on this trial; registration is described in section 15.0. Patients will not receive payment for their participation on this study. Patients are free to withdraw from the study without consequence at any time.

8.0 PRETREATMENT EVALUATION

To be completed within 28 days of starting pembrolizumab:

1. CT scan of the chest, abdomen, and pelvis with contrast. If patient is unable to receive CT contrast, or the abdominal/pelvic target lesion is indeterminate on CT scan then MRI abdomen and pelvis with contrast plus CT chest without contrast may be

perfromed. Non-contrast CT chest, abdomen, and pelvis may be used if the target lesion(s) do not require contrast for accurate measurements.

2. 12-lead Electrocardiogram (EKG).
3. Signed informed consent for study participation.
4. History and physical examination, including height, weight, vital signs (temperature, pulse rate, respiration rate, blood pressure), and ECOG performance status.
5. Serum pregnancy test for all women of childbearing potential (within 72 hours prior to receiving first dose of study medication). If the test result is positive related to pregnancy, the patient will not be allowed to participate in this study.
6. CBC with differential and platelet count, serum chemistries (Na, K, Cl, CO2, BUN, creatinine, glucose, calcium, albumin, and total protein), liver function tests (AST, ALT, alkaline phosphatase, total bilirubin), coagulation studies (PT, INR, and aPTT), and baseline TSH, fT3, and fT4 levels.
7. Serology for HepBsAg, HepBcAb and hepatitis C antibody (negative test acceptable prior to screening period).
8. Blood test for research purposes.
9. Perform baseline tumor biopsy or obtain archived tissue for research purposes.

9.0 TREATMENT/INTERVENTION PLAN

9.1 Dosing Instructions and Schedule

The treatment to be used in this trial is outlined below in Table 2.

Table 2: Trial Treatment

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

Day 1 is considered the first day of dosing. Each cycle is 3 weeks. Treatment with pembrolizumab should be administered on Day 1 of each 3 week cycle. 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 Q3W. Every effort should be made to target the infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is

permitted (i.e., infusion time is 30 minutes: -5 min/+10 min). The reason for any delay in infusion outside of the protocol specified window should be documented in the patient"s chart and recorded in the case report form. Treatment will be administered through central venous catheters or vascular access devices.

Details on the preparation and administration of pembrolizumab infusion fluid are provided in the Investigator"s Brochure.

9.2 Concomitant Medications

9.2.1 Acceptable Concomitant Medication

Investigators may prescribe concomitant medications or treatments (e.g., acetaminophen, diphenhydramine) deemed necessary to provide adequate prophylactic or supportive care and are necessary for a subject"s welfare within the standards of medical care, with the exception for those medications listed as "prohibited" in section 9.2.2.

9.2.2 Prohibited Concomitant Medications

Subjects are prohibited from receiving the following therapies during the Screening and Treatment Phase 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.

9.3 Dose Selection/Modification

9.3.1 Dose Selection (Preparation)

The rationale for selection of dose of pembrolizumab to be used in this trial is provided in section 3.3.2.3. Details on preparation and administration of pembrolizumab are provided in the Investigator"s Brochure.

9.3.2 Dose Modification (Escalation/Titration/Other)

Adverse events (both non-serious and serious) associated with pembrolizumab exposure may represent an immunologic etiology. These adverse events may occur shortly after the first dose or several months after the last dose of treatment. Pembrolizumab must be withheld for drug-related toxicities and severe or life-threatening AEs as per Table 3 below. See Section 9.4 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	Treatment Discontinuation
Diarrhea / Colitis	2-3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	4	Permanently discontinue	Permanently discontinue
AST, ALT, or Increased Bilirubin	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose
	3	Toxicity resolves to Baseline (see below) [d]	Toxicity does not resolve with therapy
	4	Permanently discontinue (see exception below)[a]	Permanently discontinue
Type 1 diabetes mellitus (if new onset) or Hyperglycemia	T1DM or 3-4	Hold pembrolizumab for new onset Type 1 diabetes mellitus or Grade 3-4 hyperglycemia associated with evidence of beta cell failure	Resume pembrolizumab when patients are clinically and metabolically stable
Hypophysitis	2-4	Toxicity resolves to Grade 0-1. Therapy with pembrolizumab can be continued while endocrine replacement therapy is instituted	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
Hyperthyroidism	3	Toxicity resolves to Grade 0-1 (see below) [d]	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	4	Permanently discontinue	Permanently discontinue
Hypothyroidism		Therapy with pembrolizumab can be continued while thyroid replacement therapy is instituted	Therapy with pembrolizumab can be continued while thyroid replacement therapy is instituted
Infusion Reaction	2[b]	Toxicity resolves to Grade 0-1	Permanently discontinue if toxicity develops despite adequate premedication
	3	Toxicity resolves to Grade 0 (see below) [d]	Toxicity does not resolve with therapy
	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	Toxicity resolves to Grade 0 (see below) [d]	Toxicity does not resolve with therapy
	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	Toxicity resolves to Grade 0	Toxicity does not resolve with therapy

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Treatment Discontinuation
		(see below)[d]	
	4	Permanently discontinue	Permanently discontinue
All Other Drug-Related Toxicity[c]	3 or Severe	Toxicity resolves to Grade 0-1 (see below)[d]	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
Myocarditis	Grade 1 or 2	Toxicity resolves to Grade 0	Based on severity of AE administer corticosteroids
	Grade 3 or 4	Permanently discontinue	Permanently discontinue

Note : Permanently discontinue for any severe or Grade 3 drug-related AE that recurs or any life-threatening event.
[a] For patients with liver metastasis who begin treatment with Grade 2 AST or ALT, if AST or ALT increases by greater than or equal to 50% relative to baseline and lasts for at least 1 week then patients should be discontinued.
[b] If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose; Refer to **Error! Reference source not found.** – Infusion Treatment Guidelines for further management details.
[c] Patients with intolerable or persistent Grade 2 drug-related AE may hold study medication at physician discretion. Permanently discontinue study drug for persistent Grade 2 adverse reactions for which treatment with study drug has been held, that do not recover to Grade 0-1 within 12 weeks of the last dose.
d Patients with grade 3 toxicity will stop therapy and be treated per section 9.4. If toxicity returns back to grade 0 after the appropriate supportive care measures, patients who have previously clinically or radiographically responded to pembrolizumab can be eligible for re-treatment with drug in the future after review and discussion of the case with the Principal Investigator.

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

9.4 Rescue Medications/Supportive Care Guidelines

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

Note: if after the evaluation the event is determined not to be related, the investigator does not need to follow the treatment guidance (as outlined below). Refer to Section 9.3 for dose modification.

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

- **Pneumonitis**:

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

- **Diarrhea/Colitis**:

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

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

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

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

- **Hyperthyroidism or Hypothyroidism**:

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

  - **Grade 2** hyperthyroidism events (and **Grade 2-4** hypothyroidism):
    - In hyperthyroidism, non-selective beta-blockers (e.g. propranolol) are suggested as initial therapy.
    - In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyroinine, is indicated per standard of care.
  - **Grade 3-4** hyperthyroidism
    - Treat with an initial dose of IV corticosteroid followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

- **Hepatic**:
  - For **Grade 2** events, monitor liver function tests more frequently until returned to baseline values (consider weekly).
    - Treat with IV or oral corticosteroids
  - For **Grade 3-4** events, treat with intravenous corticosteroids for 24 to 48 hours.
  - When symptoms improve to Grade 1 or less, a steroid taper should be started and continued over no less than 4 weeks.
- **Renal Failure or Nephritis**:
  - For **Grade 2** events, treat with corticosteroids.
  - For **Grade 3-4** events, treat with systemic corticosteroids.
  - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
- **Management of Infusion Reactions**: Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion.

  Table 4 below shows treatment guidelines for subjects who experience an infusion reaction associated with administration of pembrolizumab.

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	**Stop Infusion and monitor**	Subject may be

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for <=24 hrs	**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.**	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).
<u>Grades 3 or 4</u> 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.		

9.5 Diet/Activity/Other Considerations

9.5.1 Diet

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

9.5.2 Contraception

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

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

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

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

OR

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

OR

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

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

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

OR

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

Acceptable methods of contraception are[‡]:

Single method (one of the following is acceptable):

- intrauterine device (IUD)
- vasectomy of a female subject"s male partner

- contraceptive rod implanted into the skin

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

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

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

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

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

9.5.3 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.

If a male subject impregnates his female partner the study personnel at the site must be informed immediately.

9.5.4 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.

9.6 Subject Withdrawal/Discontinuation Criteria

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

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

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

  Note: A subject may be granted an exception to continue on treatment with confirmed radiographic progression if clinically stable or clinically improved given the potential for tumor flare on pembrolizumab.

- Unacceptable adverse experiences as described in section 9.3.2.
- 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
- Administrative reasons

After the end of treatment, each subject will be followed for 30 days for adverse event monitoring (serious adverse events will be collected for 90 days after the end of treatment). Subjects who discontinue for reasons other than progressive disease will have post-treatment follow-up for disease status until disease progression, initiating a non-study cancer treatment, withdrawing consent or becoming lost to follow-up. After documented disease progression each subject will be followed by telephone for overall survival until death, withdrawal of consent, or the end of the study, whichever occurs first.

9.7 Subject Replacement Strategy

A subject who discontinues from the trial will not be replaced.

9.8 Beginning and End of the Trial

The trial begins when the first subject signs the informed consent form. The trial ends when the last subject completes the last study related phone call or visit, discontinues from the trial, or is lost to follow-up.

9.9 Clinical Criteria for Early Trial Termination

There are no pre-specified criteria for terminating the trial early.

9.10 Research blood and biopsy specimens

9.10.1 Research blood

For the first 21 patients, blood specimens will be obtained for research purposes during screening or on day 1, then at weeks 3, 6 and 9 (± 3 days). An additional blood draw beyond week 9 is permitted based upon interesting clinical/immunological findings.

Specimens should be collected prior to drug administration. Four (4) tubes of blood are to be collected in BD Vacutainer® CPT™ Cell Preparation Tubes with Sodium Heparin. Each tube should contain approximately 10 cc of blood. Peripheral blood mononuclear cells and plasma will then be isolated per institutional practice in the Immune Monitoring Facility (IMF).

9.10.2 Research biopsy

For all patients, either a pre-treatment tumor biopsy of an index lesion will be obtained or archived tissue will be provided. Patients will be permitted to continue enrollment and treatment on protocol in the event that insufficient material was obtained from the biopsy.

In patients who exhibit a PR or a CR and who proceed to surgical resection, surgically resected tissue will be collected after obtaining patient consent. In patients with tumor response who do not have disease amenable to surgical resection, an optional core biopsy will be requested and performed after obtaining patient consent. Next-generation sequencing of the tumor tissue may be considered for these responder patients, however if next-generation sequencing is pursued, patients will be separately consented to protocol #12-245 to have MSK-IMPACT testing performed through our institutional protocol.

9.10.3 Correlative studies

Pharmacodynamic changes may be evaluated for associations with clinical activity, and safety (adverse event) data. Core biopsies may be used for correlative studies such as IHC, tumor mutation analysis, proteomic analysis, and immunodiversity. PDL-1 immunohistochemistry will be done by a Merck designated laboratory. Other assessment will be done at MSKCC.

9.10.3.1 Whole Blood

Flow cytometry will be performed at baseline and during treatment to assess baseline and changes in composition/activation status of lymphocyte subsets present in peripheral blood mononuclear cell preparations (PBMCs). Lymphocyte subsets to be assayed may include, but are not limited to CD8+ and CD4+ T-cell subsets (activated; effector/memory; regulatory) and populations of those cells as defined by the expression of activation, exhaustion, or signaling markers such as ICOS, HLA-DR, PD-1, CTLA-4, and/or intracellular IFNγ. NK cell populations may be monitored in a similar fashion with a focus on characterizing subsets defined by the expression of activation markers (e.g. NKG2D; IL-21R) and/or by markers that are associated with the potential of NK cells to lyse target cells (e.g., CD107a, granzyme, perforin). Additional flow cytometry-based assays will focus on defining and monitoring the abundance of myeloid-derived suppressor cells (MDSCs), a cell type which appears to negatively impact anti-tumor

activity and which has been shown to promote immune escape by limiting activated CD8 T-cell infiltration into the tumor microenvironment [27].

Immune cells may be evaluated using HLA-A2-restricted tetramer assays to detect and quantify the presence of T cells directed against specific antigens which are anticipated to be presented to the immune system due to study treatment. Detecting on-treatment increases in these T cell populations may be considered evidence of adaptive immune responses in ACC.

9.10.3.2 Plasma

To understand the prevalence of circulating proteins and the impact they may have on the clinical activity and/or safety of pembrolizumab treatment, the protein concentrations of a panel of cytokines, chemokines, and other relevant immunomodulatory, soluble factors may be investigated by ELISA and/or other relevant multiplex-based protein assay methods. Examples of analytes to be assessed may include but are not limited to factors induced by IFNγ signaling (e.g., T cell chemoattractants CXCL9; CXCL10) and other factors generally involved in inflammatory processes. Plasma may be used also to assess the presence and/or concentration of anti-tumor antibodies using a mulitplex platform such as Invitrogen"s Protoarray platform(c). Levels of sPD-L1 in peripheral blood may also be assessed.

9.10.3.4 Tissue Biopsies and/or archived tissue

The presence of TILs within tumors in response to pembrolizumab treatment will be evaluated at baseline and on biopsies or surgical specimens from responder patients. Archived tissue (up to 20 x 5 μm slides) and biopsy tissue may be analyzed using immunohistochemistry for PD-L1 expression and other immune-related genes, and gene expression (microarray and/or RT- QPCR) research platforms. Laser Capture Microdissection may be utilized to enrich specific regions of tumor material for use in similar or additional downstream applications, which may include in-situ hybridization, flow cytometry, ELISA, and/or assessment of miRNA. In all cases, the goal may be to determine the abundance of a battery of immunoregulatory genes or proteins associated with cancer cells and/or cancer-interacting lymphocytes derived from biopsied material. Other biomarkers may be evaluated as determined by additional data. Remaining specimens may be stored for future studies related to ACC immunity.

10.0 EVALUATION DURING TREATMENT/INTERVENTION

Study Calendar

Period	Screening	Treatment							End of study visit
Cycle[1]	<28 days[2]	1[13]	2	3	4	5	6	7+	
Week		0	3	6	9	12	15	18+	
Informed consent	x								
Medical history	x								
EKG	x								
CT/MRI[3]	x				x			x	x
Height[4]	x								
Physical examination	x	x	x	x	x	x	x	x	x

Vital signs /Performance status[4]	x	x	x	x	x	x	x	x	x
Report medications	x	x	x	x	x	x	x	x	x
Report side effects			x	x	x	x	x	x	x
CBC[5,6]	x	x	x	x	x	x	x	x	x
Comp[5,7]	x	x	x	x	x	x	x	x	x
Coagulation studies (PT, INR, aPTT)	x								
Thyroid function (TSH, fT3,fT4)	x			x		x		odd cycles	
Hepatitis B and C[8]	x								
Pregnancy test if female (Serum)[9]	x								
Research blood tests[10]	x		x	x	x				
Obtain archived tissue[11]	x								
Research tumor biopsy[12]	x		On therapy if partial or complete response						
Pembrolizumab		x	x	x	x	x	x	x	

1. Each cycle is approximately 3 weeks in duration, corresponds to 1 completed treatment.
2. Procedures must be performed within 28 days prior to dose 1 of Pembrolizumab on Day 1.
3. CT or MRI will be performed during screening, then at 9 week (±1 wk) intervals and at final visit if more than 4 weeks from prior imaging. If patient is unable to receive CT contrast or the abdominal/pelvic target lesion is indeterminate on CT then MRI with contrast (abdomen and pelvis) plus CT without contrast (chest) may be performed.
4. Vital signs to include heart rate, respiratory rate, blood pressure, and weight.
5. Blood to be collected prior to dosing any study medications.
6. Hematology to include standard complete blood cell (CBC) panel.
7. Comprehensive metabolic panel included sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, total protein, albumin, bilirubin, alkaline phosphatase, AST, ALT, calcium.
8. Serology for HepBs Ag, HepBcAb and hepatitis C antibody (unless previously tested negative).
9. Serum pregnancy test is required within 72 hours prior to starting Pembrolizumab.
10. Blood draws for research purposes performed during screening or day 1, then weeks 3, 6 and 9 for the first 21 patients enrolled.
11. Up to 20 x 5 μm slides (unstained) will be requested on all patients for research purposes.
12. Research tumor biopsy will be performed as baseline (if archived tissue is not available) and while on treatment for responder patients.
13. CBC & Comp must be performed on day of first treatment or within 3 days of Cycle 1 Week 0.

11.0 TOXICITIES/SIDE EFFECTS

The most commonly reported treatment emergent AEs related to pembrolizumab are fatigue (43.8%), nausea (26.7%), cough (25.3%), pruritus (24.6%), diarrhea (22.3%) and rash (21.5%). Immune-related adverse events were reported in 21.4% of melanoma patients; most of these events (15.8%) were considered drug-related by the investigator. The most commonly reported, immune-related adverse events across the dose-schedules are rash (3.2%), pruritus (2.9%), vitiligo (2.9%), hypothyroidism (2.7%), arthralgia (2.2%), diarrhea (2.2%), and pneumonitis (1.9%).

11.1 SAFETY MONITORING

Subjects will be evaluated for occurrence of AEs at each visit. Events will be characterized and reported as described below. Safety will also be monitored by performing physical exams and routine laboratory procedures.

11.1.1 Adverse Events and Serious Adverse Events

Definitions of AEs, non-serious AEs, and serious adverse events (SAEs) are provided in this section. Additionally, provided in the sections below are reporting guidelines for any AE or SAE occurring during this study.

Definition of Adverse Event and Non-Serious Adverse Event

The following definition of AE will be used for the study: "Any untoward medical occurrence in a subject 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), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to medicinal (investigational) product."

This definition includes any abnormalities or anomalies that were not seen at baseline or which worsened during the course of the study, if present at baseline.

A "non-serious" adverse event is any event that does not meet the definition of "serious adverse event" as presented, below.

Reporting and Treating Non-Serious Events

It is the responsibility of the investigator to perform regular assessments for AEs. Subjects will be regularly queried about the occurrence of any AEs and will be monitored throughout the study for reactions to study drug and/or study procedures. The investigator and clinical staff will record all AEs, whether volunteered by or elicited from the subject, at any time during a subject's participation in the study. All events occurring prior to the first dosing will be recorded on the Medical History page of the CRDB. All AEs occurring at any time after the initiation of the first dose of study drug will be recorded on the Adverse Event page of the CRDB. AEs will be recorded according to "Common Terminology Criteria for Adverse Events" v4.0 (CTCAE). AEs meeting the definition of SAE require additional reporting as described below.

All subjects experiencing an AE will be evaluated by the investigator and monitored until resolution of the events or until the investigator deems the event clinically stable and/or at an acceptable level. Unless the event requires hospitalization (SAE), medical treatment will be provided to the subjects at the unit and treatment medication and/or medical procedures will be provided per the treating-investigator's clinical discretion. All clinically significant AEs, including clinically significant laboratory abnormalities, will be followed until resolution. SAEs require special reporting in addition to documentation in the CRDB as described below.

All AEs, including SAEs, must be recorded in the CRDB. Events occurring prior to initiation of first dose should be recorded on the Medical History page of the CRDB. Any AE occurring at initiation of first dose and or during any point throughout the study should be recorded on the Adverse Event page of the CRDB. AEs should be recorded in the CRDB using the medical terminology found in the source documentation. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology. It is the investigator's responsibility to provide

his/her assessment of the relationship of the event to the study drug and the severity of the event using the following scales:

- Relationship

➢ *Unrelated*: The AE is clearly attributable to a concurrent illness, concurrent medication, clinical state, or environmental factor other than the investigative agent.

➢ *Unlikely*: The occurrence of the AE does not follow the study in a temporal sequence and/or based upon available subject information, e.g., medical history, disease process, known pharmacology of drug, a relationship between the drug and AE is unlikely.

➢ *Possible*: The AE follows a reasonable temporal sequence from the time of study drug administration, but it is possible that other factors; e.g., subject"s clinical state or concomitant mediations, environmental factors, or the drug"s pharmacology may have caused the AE.

➢ *Probable*: The AE follows a reasonable temporal sequence from the time of study drug administration, follows a known response pattern of the medication class, and cannot be reasonably explained by other factors.

- Severity

The severity of all adverse events should be graded according to the Common Terminology Criteria for Adverse Events (CTCAE) v4.0. For those adverse events not listed in the CTCAE, the following grading system should be employed:

➢ *Mild* (CTCAE Grade 1): Transient symptoms, awareness of sign/symptom, but easily tolerated and no interference with subject"s daily activities

➢ *Moderate* (CTCAE Grade 2): Marked signs/symptoms that interfere with subject"s usual activities, but still acceptable

➢ *Severe* (CTCAE Grade 3): Incapacitating signs/symptoms which cause considerable interference with the subject"s daily activities, unacceptable

➢ *Life-threatening* (CTCAE Grade 4): Life-threatening of disabling AE

➢ *Death* (CTCAE Grade 5): Death-related AE. See CTCAE Guidelines for assigning Grade 5.

Definition of Serious Adverse Event

The following definition of SAE applies for the study: "A serious AE means any AE occurring at any dose that results in any of the following outcomes: death, a life-threatening AE, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, a congenital anomaly/birth defect, or overdose of study drug. Important medical events that may not result in death, be life threatening, or require hospitalization may be considered a serious AE when, based upon appropriate medical judgment, they may jeopardize the subject or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. A life-threatening AE is any AE that places the subject or

subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred (e.g., it does not include a reaction that, had it occurred in a more severe form, might have caused death)." Reporting and Treating Serious Adverse Events as per section 17.2.

Pregnancies

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

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

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

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

11.1.3 Other Events of Special Interest

Hepatic Function Abnormality

Hepatic function abnormality is defined as any increase in ALT or AST to greater than 3 × ULN and concurrent increase in bilirubin to greater than 2 × ULN. Concurrent findings are those that derive from a single blood draw or from separate blood draws taken within 8 days of each other. Follow-up investigations and inquiries will be initiated promptly by the investigational site to determine whether the findings are reproducible and/or whether there is objective evidence that clearly supports causation by a disease (e.g., cholelithiasis and bile duct obstruction with distended gallbladder) or an agent other than the investigational product.

Events of hepatic function abnormality (as defined above) should be recorded according to the definitions of AE and SAE:

- If an event of hepatic function abnormality is considered to be related to a pre-existing condition and does not represent a worsening of this condition and/or is considered to be within the range of normal physiological fluctuation for the subject, the event does not meet the definition of an AE and does not need to be recorded as such.

- If a definitive diagnosis for an underlying condition unrelated to the investigational product is established for an event of hepatic function abnormality, the diagnosis should be recorded as an AE/SAE.
- If no definitive diagnosis is determined for an event of hepatic function abnormality, the term "hepatic function abnormal" should be used to report the AE/SAE.

Definition of an Overdose for This Protocol and Reporting of Overdose 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)

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

For the purposes of this study, patients will be evaluated for response every 3 cycles (approximately 9 weeks), or as clincially indicated if interim toxicity occurs mandating cancer staging re-assessment. RECIST v1.1 criteria will be used.

CT scan with contrast of the chest, abdomen, and pelvis

- CT scans should be performed with contiguous cuts in slice thickness of 5 mm or less. Spiral CT should be performed using a 5-mm contiguous reconstruction algorithm.

MRI scans

- MRI of the abdomen and pelvis is acceptable for measurement of lesions provided that the same anatomical plane is used for serial assessments. If possible, the same imaging device should be used for serial evaluations. In case of MRI, measurements will be preferably performed in the axial (transverse) plane on contrast-enhanced T1-weighted images. However, there are no specific sequence recommendations.

Measurability of Tumor Lesions

Tumor lesions will be categorized as follows:

- **Measurable Lesions -** Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:
    - 10 mm by CT scan (irrespective of scanner type) and MRI (no less than double the slice thickness and a minimum of 10 mm)
    - 10 mm caliper measurement by clinical exam (when superficial)
    - Malignant lymph nodes are considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm).
- **Nonmeasurable Lesions -** Nonmeasurable lesions are defined as all other lesions (or sites of disease), including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis). Lesions considered truly nonmeasurable include the following: leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.
- **Target Lesions -** All lesions up to a maximum of 5 lesions total (and a maximum of 2 lesions per organ) representative of all involved organs should be identified as target lesions. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.
- **Non-target Lesions -** It is possible to record multiple nontarget lesions involving the same organ as a single item on the case record form (e.g., “multiple enlarged pelvic lymph nodes” or “multiple liver metastases”)

Response Criteria

Evaluation of Target Lesions

- **Complete Response -** Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm (the sum may not be “0” if there are target nodes).
- **Partial Response -** At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.
- **Progressive Disease -** At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression.)
- **Stable Disease -** Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum of diameters while on study.

Evaluation of Non-target Lesions

- **Complete Response -** Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis).
- **Non-complete response/Non-progressive disease -** Persistence of 1 or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
- **Progressive Disease -** Unequivocal progression of existing non-target lesions will be defined as the overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. In the absence of measurable disease, change in non-measurable disease comparable in magnitude to the increase that would be required to declare PD for measurable disease. Examples include an increase in a pleural effusion from „trace" to „large," an increase in lymphangitic disease from localized to widespread.

Appearance of New Lesions

The appearance of new lesions is considered PD according to RECIST v1.1 guidelines. Considering the unique response kinetics that have been observed with immunotherapy, *new lesions may not represent true disease progression.* In the absence of rapid clinical deterioration, subjects may continue to receive treatment with pembrolizumab.

Evaluation of Overall Response

Table 12 provides overall responses for all possible combinations of tumor responses in target and non-target lesions with or without the appearance of new lesions.

Table 5: Evaluation of Overall Response

Target Lesions	Non-target Lesions	New Lesions	Overall Response
Complete response	Complete response	No	Complete response
Complete response	Not evaluable	No	Partial response
Complete response	Non-complete response / non-progressive disease	No	Partial response
Partial response	Non-progressive disease and not evaluable [a]	No	Partial response
Stable disease	Non-progressive disease and not evaluable [a]	No	Stable disease
Not all evaluated	Non-progressive disease	No	Not evaluable
Progressive disease	Any	Yes/No	Progressive disease
Any	Progressive disease	Yes/No	Progressive disease
Any	Any	Yes	Progressive disease

[a] Not evaluable is defined as either when no or only a subset of lesion measurements are made at an assessment.

13.0 CRITERIA FOR REMOVAL FROM STUDY

In the absence of serious toxicity or complications, all patients will continue treatment until evidence of disease progression, or for up to 24 months, whichever is first. In the absence of treatment delays due to adverse event(s), treatment may continue until one of the following criteria applies:

- Progression of disease. Patients will be allowed to stay on study in the setting of progression of disease, if they appear to be deriving clinical benefit, per the PI's discretion, given the potential for tumor flare.
- 24 months of treatment with pembrolizumab. These patients will be eligible to receive an additional 12 months of treatment in the future, should they experience disease progression at a later date.
- Development of an intercurrent medical condition or need for concomitant treatment that precludes further participation in the trial.
- Unacceptable toxicity or any adverse event that precludes further participation in the trial.
- The investigator removes the patient from the trial in the best interests of the patient.
- Patient death.
- Study completion or discontinuation for any reason.
- Patient withdraws consent to continued participation in the trial or is lost to follow up.

Subjects who are permanently discontinued from receiving investigational product will return for end of study visit, unless consent is withdrawn, the subject is lost to follow-up or begins another treatment. All subjects will be followed for survival by phone every 3 months until death or withdrawal of consent.

If consent is withdrawn, the subject will not receive any further investigational product or further study observation.

14.0 BIOSTATISTICS

Response: The null and alternative overall response rates used to determine the sample size calculation as follows:

The primary endpoint of this trial is to assess best overall response rate of pembrolizumab using RECIST v1.1 in subjects with unresectable or stage IV ACC. A Simon minimax 2 stage design will be employed to test the null hypothesis that the true response rate is ≤ 12% versus the alternative hypothesis that the true response rate is at least 29% with type I and II error rates of 10% each. In the first stage, 21 patients will be enrolled. If at least 3 out of 21 patients respond (PR or CR), then the study will be expanded to enroll an additional 18 patients for a total of 39 patients. At the end of the study, ≥ 8 of 39 tumor responses by RECIST 1.1 are observed, further investigation of pembrolizumab will be considered worthwhile. With 39 patients, we anticipate an improvement from 12% to 29%. The probability of early termination is 53%.

ORR of 12% comes from the FIRMACT which is the only randomized study in ACC. In that study, ORR in the control arm was 9% versus approximately 20% in the experimental arm, however, the rate of serious adverse events on the experimental arm was 58%. Our patient population in this current study includes patients that are untreated and treated with platinum based therapy. For that reason, we said that an ORR ≤ 12% would be unworthy of further investigation.[10]

Secondary outcomes, including safety, the additional measures of immune system activation, and exploratory objectives will also be summarized.

The study will be complete when all subjects have either completed 24 months of drug therapy, progressed, or discontinued from the study for other reasons. The accrual time is estimated to be 2 years. This study requires accrual of a minimum of 21 subjects and up to a maximum of 39 subjects if the study is expanded to the second stage. Patients that have been enrolled and then deemed ineligible prior to starting treatment may be replaced.

Antitumor Activity

Assessments of antitumor activity will be based on ORR. RECIST v1.1 with modifications to account for the unique response patterns observed with immunotherapy will be used to determine tumor response.[28]

The ORR is defined as the proportion of subjects with CR or PR based on RECIST criteria. The exact 95% CI of ORR will be estimated using the binomial distribution. EFS will be measured from the start of treatment with pembrolizumab until the documentation of disease recurrence (for those patients who proceed to surgical resection after treatment), progression, or death due to any cause, whichever occurs first. EFS will be censored on the date of last tumor assessment documenting absence of tumor progression for subjects who are still alive prior to data cutoff, dropout, or the initiation of alternate anticancer treatment. Subjects having no tumor assessments

after the start of treatment with pembrolizumab will have EFS censored on the first date of treatment with pembrolizumab. EFS will be evaluated using the Kaplan-Meier method. OS will be determined as the time from the start of treatment with pembrolizumab until death. For subjects who are alive at the end of study or lost to follow-up, OS will be censored on the last date when subjects are known to be alive. The OS will be evaluated using the Kaplan-Meier method.

Safety and Tolerability Analyses

All recorded adverse events will be listed and tabulated by system organ class, preferred term and treatment. Any significant vital signs and clinical laboratory test results will be listed and summarized. Any significant physical examination findings, and clinical laboratory results will be listed.

Biomarker Analysis

Exploratory research studies that will be done to evaluate the effect of pembrolizumab will be performed using research blood draws and tumor biopsies. Research bloods are collected at baseline and weeks 3, 6, and 9. Tumor biopsy is performed at baseline (if archival tissue is not available) and in patients where the tumor responds (and at the time of response).

Endpoints from blood tissue -The pharmacodynamic effect of pembrolizumab on TILs, such as CD4+ and CD8+ T-cells, will be assessed by summary statistics, and investigated graphically to explore patterns of change. The pharmacodynamic effect of pembrolizumab on markers in peripheral blood, such as ICOS, HLA-DR, PD-1, CTLA-4; and, serum proteins, such as CXCL9; CXCL10, will be assessed by summary statistics, and investigated graphically to explore patterns of change over time, i.e.: pretreatment, then week 3, week 6 and week 9.

In addition, the relationship of TIL changes and tumor marker expression with measures of peripheral blood markers will be summarized descriptively.

Endpoints from biopsy tissue - Expression of tumor markers PD-L1, from pre-treatment to post-treatment biopsy specimens will also be assessed by summary statistics in those patients that achieve a response to therapy and either have a resection or consent to a biopsy

Associations between the markers and response by RECIST will be explored.

Fisher"s exact test will be employed to assess associations between categorical variables while Spearman's rank correlation will be used for continuous variables. Wilcoxon signed rank test will be used to test for differences in continuous expression tumor markers between pre- and post-treatment specimens while McNemar"s test will be used to assess these relationships for binary markers.

15.0 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.1 Research Participant Registration

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

Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures.

During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist.

All participants must be registered through the Protocol Participant Registration (PPR) Office at Memorial Sloan Kettering Cancer Center. PPR is available Monday through Friday from 8:30am – 5:30pm at 646-735-8000. Registrations must be submitted via the PPR Electronic Registration System (http://ppr/). The completed signature page of the written consent/RA or verbal script/RA, a completed Eligibility Checklist and other relevant documents must be uploaded via the PPR Electronic Registration System.

15.2 Randomization

Not applicable.

16.0 DATA MANAGEMENT ISSUES

A Research Study Assistant (RSA) will be assigned to the study. The responsibilities of the RSA include project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordinate the activities of the protocol study team.

The data collected for this study will be entered into a secure database (Clinical Research Database, CRDB). Source documentation will be available to support the computerized patient record.

16.1 Quality Assurance

Weekly registration reports will be generated to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and extent, and accuracy of evaluations and follow-up will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action.

Random-sample data quality and protocol compliance audits will be conducted by the study team, at a minimum of two times per year, more frequently if indicated.

16.2 Data and Safety Monitoring

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan Kettering Cancer Center were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled “Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials” which can be found at: http://cancertrials.nci.nih.gov/researchers/dsm/index.html. The DSM Plans at MSKCC were established and are monitored by the Office of Clinical Research. The MSKCC Data and Safety Monitoring Plans can be found on the MSKCC Intranet at:

http://mskweb5.mskcc.org/intranet/_assets/_tables/content/359689/Data_safety%20Monitoring07.pdf

There are several different mechanisms by which clinical trials are monitored for data, safety and quality. There are institutional processes in place for quality assurance (e.g., protocol monitoring, compliance and data verification audits, therapeutic response, and staff education on clinical research QA) and departmental procedures for quality control, and there are two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees: *Data and Safety Monitoring Committee (DSMC)* for Phase I and II clinical trials, and the *Data and Safety Monitoring Board (DSMB)* for Phase III clinical trials, report to the Center"s Research Council and Institutional Review Board.

During the protocol development and review process, each protocol will be assessed for its level of risk and degree of monitoring required. Every type of protocol (e.g., NIH sponsored, in-house sponsored, industrial sponsored, NCI cooperative group, etc.) will be addressed and the monitoring procedures will be established at the time of protocol activation.

17.0 PROTECTION OF HUMAN SUBJECTS

All the patients will be required to sign an IRB-approved informed consent and will have all their questions fully addressed before enrolling in the study. During informed consent, it will be made clear to the patient that participation is voluntary. All the data will be confidential, maintained in a password protected electronic database and will comply with all HIPAA guidelines.

Benefits: It is possible that this treatment will result in shrinkage of ACC or in a stabilization of an otherwise progressing disease. It is not known, of course, whether these or any other favorable events will occur.

Costs: The patient will be responsible for the costs of standard medical care, including, CT or MRI scans, all drug administration fees and all hospitalizations, even for complications of treatment. Pembrolizumab will be supplied to patients by Merck at no cost. Patients will not be responsible for the costs of blood procurement obtained for research purposes or the cost for obtaining the tumor biopsy for research purposes.

Incentives: No incentives will be offered to patients/subjects for participation in the study.

Alternatives/options for treatment: Patients may be eligible for other investigational studies, standard treatment options, or focus on palliative care options.

Confidentiality: Every effort will be made to maintain patient confidentiality. Research and hospital records are confidential. Patient's name or any other personally identifying information will not be used in reports or publications resulting from this study. The Food and Drug Administration or other authorized agencies (e.g., qualified monitors) may review patients' records and pathology slides, as required.

17.1 Privacy

MSK's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board (IRB/PB).

17.2 Serious Adverse Event (SAE) Reporting

An adverse event is considered serious if it results in ANY of the following outcomes:

- Death
- A life-threatening adverse event
- An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization

- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

Note: Hospital admission for a planned procedure/disease treatment is not considered an SAE.

SAE reporting is required as soon as the participant signs consent. SAE reporting is required for 30-days after the participant's last investigational treatment or intervention. Any events that occur after the 30-day period and that are at least possibly related to protocol treatment must be reported.

If an SAE requires submission to the IRB office per IRB SOP RR-408 „Reporting of Serious Adverse Events", the SAE report must be sent to the IRB within 5 calendar days of the event. The IRB requires a Clinical Research Database (CRDB) SAE report be submitted electronically to the SAE Office as follows:

For IND/IDE trials: Reports that include a Grade 5 SAE should be sent to saegrade5@mskcc.org. All other reports should be sent to saemskind@mskcc.org.

For all other trials: Reports that include a Grade 5 SAE should be sent to saegrade5@mskcc.org. All other reports should be sent to sae@mskcc.org.

The report should contain the following information:

Fields populated from CRDB:

- Subject's initials
- Medical record number
- Disease/histology (if applicable)
- Protocol number and title

Data needing to be entered:

- The date the adverse event occurred
- The adverse event
- The grade of the event
- Relationship of the adverse event to the treatment (drug, device, or intervention)
- If the AE was expected
- The severity of the AE
- The intervention
- Detailed text that includes the following

  - A explanation of how the AE was handled
  - A description of the subject"s condition
  - Indication if the subject remains on the study
- If an amendment will need to be made to the protocol and/or consent form
- If the SAE is an Unanticipated Problem

The PI's signature and the date it was signed are required on the completed report.

17.2.1 For the time period beginning when the consent form is signed until treatment allocation/randomization, any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study that occurs to any subject must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study whether or not related to the Merck product, must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety.

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

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

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

A copy of all 15 Day Reports and Annual Progress Reports is submitted as required by FDA, 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.

Events of Clinical Interest

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

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

For the time period beginning at treatment allocation/randomization through 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, any ECI, or follow up to an ECI, whether or not related to Merck product, must be reported within 24 hours to the Sponsor and within 24 hours to Merck Global Safety.

Events of clinical interest for this trial include:

1. an overdose of Merck product, as defined in Section 11.1.3 - 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.

18.0 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

19.0 REFERENCES

1. Glover, A.R., et al., *Current management options for recurrent adrenocortical carcinoma.* Onco Targets Ther, 2013. **6**: p. 635-43.
2. Lafemina, J. and M.F. Brennan, *Adrenocortical carcinoma: past, present, and future.* J Surg Oncol, 2012. **106**(5): p. 586-94.
3. Schulick, R.D. and M.F. Brennan, *Long-term survival after complete resection and repeat resection in patients with adrenocortical carcinoma.* Ann Surg Oncol, 1999. **6**(8): p. 719-26.
4. Luton, J.P., et al., *Clinical features of adrenocortical carcinoma, prognostic factors, and the effect of mitotane therapy.* N Engl J Med, 1990. **322**(17): p. 1195-201.
5. Hutter, A.M., Jr. and D.E. Kayhoe, *Adrenal cortical carcinoma. Clinical features of 138 patients.* Am J Med, 1966. **41**(4): p. 572-80.
6. Lubitz, J.A., L. Freeman, and R. Okun, *Mitotane use in inoperable adrenal cortical carcinoma.* JAMA, 1973. **223**(10): p. 1109-12.
7. Macfarlane, D.A., *Cancer of the adrenal cortex; the natural history, prognosis and treatment in a study of fifty-five cases.* Ann R Coll Surg Engl, 1958. **23**(3): p. 155-86.
8. Bodie, B., et al., *The Cleveland Clinic experience with adrenal cortical carcinoma.* J Urol, 1989. **141**(2): p. 257-60.
9. Jensen, J.C., et al., *Recurrent or metastatic disease in select patients with adrenocortical carcinoma. Aggressive resection vs chemotherapy.* Arch Surg, 1991. **126**(4): p. 457-61.
10. Fassnacht, M., et al., *Combination chemotherapy in advanced adrenocortical carcinoma.* N Engl J Med, 2012. **366**(23): p. 2189-97.
11. O'Sullivan, C., et al., *The VEGF inhibitor axitinib has limited effectiveness as a therapy for adrenocortical cancer.* J Clin Endocrinol Metab, 2014. **99**(4): p. 1291-7.
12. Berruti, A., et al., *Phase II study of weekly paclitaxel and sorafenib as second/third-line therapy in patients with adrenocortical carcinoma.* Eur J Endocrinol, 2012. **166**(3): p. 451-8.
13. Kroiss, M., et al., *Sunitinib in refractory adrenocortical carcinoma: a phase II, single-arm, open-label trial.* J Clin Endocrinol Metab, 2012. **97**(10): p. 3495-503.
14. Ryder, M., et al., *Endocrine-related adverse events following ipilimumab in patients with advanced melanoma: a comprehensive retrospective review from a single institution.* Endocr Relat Cancer, 2014. **21**(2): p. 371-81.
15. Yamamoto, Y., et al., *Cytotoxic activity and T cell receptor repertoire in tumor-infiltrating lymphocytes of adrenal cell carcinomas.* Cancer Immunol Immunother, 1993. **37**(3): p. 163-8.
16. Fay, A.P., et al., *Programmed death ligand-1 expression in adrenocortical carcinoma: an exploratory biomarker study.* J Immunother Cancer, 2015. **3**: p. 3.
17. Assie, G., et al., *Integrated genomic characterization of adrenocortical carcinoma.* Nat Genet, 2014. **46**(6): p. 607-12.
18. Snyder, A., et al., *Genetic basis for clinical response to CTLA-4 blockade in melanoma.* N Engl J Med, 2014. **371**(23): p. 2189-99.
19. Brown, S.D., et al., *Neo-antigens predicted by tumor genome meta-analysis correlate with increased patient survival.* Genome Res, 2014. **24**(5): p. 743-50.

20. Rottembourg, D., et al., *21-Hydroxylase epitopes are targeted by CD8 T cells in autoimmune Addison's disease.* J Autoimmun, 2010. **35**(4): p. 309-15.
21. Ortmann, D., et al., *Steroidogenic acute regulatory (StAR)-directed immunotherapy protects against tumor growth of StAR-expressing Sp2-0 cells in a rodent adrenocortical carcinoma model.* Endocrinology, 2004. **145**(4): p. 1760-6.
22. Papotti, M., et al., *Pathology of the adrenal cortex: a reappraisal of the past 25 years focusing on adrenal cortical tumors.* Endocr Pathol, 2014. **25**(1): p. 35-48.
23. Sharpe, A.H. and G.J. Freeman, *The B7-CD28 superfamily.* Nat Rev Immunol, 2002. **2**(2): p. 116-26.
24. Dong, H., et al., *Tumor-associated B7-H1 promotes T-cell apoptosis: a potential mechanism of immune evasion.* Nat Med, 2002. **8**(8): p. 793-800.
25. Brown, J.A., et al., *Blockade of programmed death-1 ligands on dendritic cells enhances T cell activation and cytokine production.* J Immunol, 2003. **170**(3): p. 1257-66.
26. Francisco, L.M., P.T. Sage, and A.H. Sharpe, *The PD-1 pathway in tolerance and autoimmunity.* Immunol Rev, 2010. **236**: p. 219-42.
27. Lesokhin, A.M., et al., *Monocytic CCR2(+) myeloid-derived suppressor cells promote immune escape by limiting activated CD8 T-cell infiltration into the tumor microenvironment.* Cancer Res, 2012. **72**(4): p. 876-86.
28. Eisenhauer, E.A., et al., *New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1).* Eur J Cancer, 2009. **45**(2): p. 228-47.

20.0 APPENDICES

Appendix A: Investigator"s Brochure