Coordinated High Dose Interleukin-2 (aldesleukin, Proleukin) and Pembrolizumab (anti-PD1, Keytruda) for Therapy of Metastatic Kidney Cancer

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TITLE:

Coordinated high dose interleukin-2 (aldesleukin, Proleukin™) and pembrolizumab (anti-PD1, Keytruda™) for therapy of metastatic kidney cancer

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PROTOCOL APPROVAL

Coordinated high dose interleukin-2 (aldesleukin, Proleukin™) and pembrolizumab (anti-PD1, Keytruda™) for therapy of metastatic kidney cancer

Protocol: IIT15PLK02

Original Protocol Date: 9/30/15

This protocol has been reviewed and approved by

Prometheus:

Date

Principal Investigator:

Jad Chahoud MD

Date

Moffitt Cancer Center

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1.0 TRIAL SUMMARY

FIGURE 1: BLOCK FORMAT TRIAL SUMMARY

Abbreviated Title	Kidney cancer treatment: 5-in-a-row IL2 w/ pembrolizumab
Trial Phase	Feasibility (phase II)
Clinical Indication	Metastatic kidney cancer
Trial Type	Treatment
Type of control	Historical
Route of administration	IV: pembrolizumab (Keytruda™) IV: IL-2 (aldesleukin; Proleukin™)
Trial Blinding	None—open label
Treatment Groups	Single dose level
Number of trial subjects	26
Estimated enrollment period	4/2017 to 3/2019
Estimated duration of trial	3 years
Duration of Participation	9 months treatment. 1-year landmark evaluation.

Funding supported by: Prometheus Labs, San Diego, CA.

Drug supplied: Pembrolizumab [MK-3475] supplied by Merck.

Aldesleukin IL-2: Commercial supply.

Regulatory Sponsor: Moffitt Cancer Center

Data management: Moffitt Cancer Center

Narrative synopsis

Medication background: IL-2 is a cytokine drug and PD-1 antibodies are immunotherapy drugs with demonstrated activity in kidney cancer, including a few patients with complete responses. Whereas IL-2 binds to an activating receptor (CD25/CD122/CD132; IL-2Rαβγ) on lymphocytes, and has decades of experience in clinical application, PD-1 antibodies such as pembrolizumab bind to and block the function of PD-1 receptors (CD 279) that decrease activation that would be prevented by ligation of PD-L1 (CD274; B7-H1), and are relative new entrants in oncologic therapeutics. The downstream physiologic events for either medication are well-studied, but complex, with changes of behavior of multiple, and varying, subsets of lymphocytes that may ultimately mediate the therapeutic effect. There is not a particular specific pathway that can be claimed to be a simple mechanism of action, for either. Similarly prediction of for whom there will be a major therapeutic response remains an inexact process, despite significant efforts in the separate experiences. While IL-2 therapy (referring to Proleukin™ prescribing information) requires a controlled, experienced setting for safe administration, pembrolizumab is a relatively simpler infusion process (as described on the Keytruda™ prescribing information), with outpatient infusions typically with no immediate complications. Immune-related or cytokine-related side effects of the two medicines also differ as far as kinetics. Typically (even when severe), IL-2 side effect subside within days of cessation of administration; immune activation events of PD-1 directed immunotherapy may require active therapy with corticosteroids or other immunosuppressants, for weeks or more.

Outcome goals background: As a fundamental goal of anticancer therapy, the durable, complete response remains a gold standard. In this prospective protocol concurrent, coordinated use of these two immunotherapies will be administered to patients in a prospective series, in the setting of an experienced IL-2 center. The use of a single-arm trial format will accommodate the key scientific developmental question of feasibility. An estimate of response completeness and durablility will also be calculated. Response and side effect experiences can be tabulated, but without the scale of a trial with a randomized treatment assignment, cross trial comparisons remain mathematically limited.

Treatment plan: Patients with clear cell kidney cancer will be included; the extent of recent prior pretreatment will be restricted, consistent with the usual use of IL-2 (initial therapy) or with the indication of a related medication (nivolumab: after anti-angiogenic therapy). There are four blocks of 9 weeks (3 pembrolizumab infusions each, and interval radiologic and clinical disease assesment); the second and third blocks have concurrent administration of IL-2, with 20 planned doses divided into four courses of 5 doses each; and then the protocol treatment is discontinued which will address unmaintained durability for responses.This IL-2 schedule differs from the Proleukin™ prescribing information in which two courses of 14 doses each are used, by having more planned breaks, but the cumulative planned dose (20 IL-2 doses/block) is comparable to the typical delivered dose of the 14-dose plan. In the prior institutional experience with the 5-in-a-row IL-2 treatment as monotherapy, the 5 year OS was 65% among 20 kidney cancer subjects.

2.1 TRIAL DESIGN

2.2 Trial Design

Overall schedule plan: The treatment is organized into blocks of 9 weeks, with pembrolizumab treatment planned for weeks 1, 4 and 7. On the second and third blocks, interleukin-2 is added, for 5 doses at a time, one dose every 8 hours, on a weekly schedule on the two weeks after the week 1 and the week 4 pembrolizumab doses. This works out to a plan of 20 doses per 9 week block. The fourth block is again pembrolizumab monotherapy, as was the first. If delays occur prior to the 2nd or 3rd block, up to one additional 3 week (one dose) pembrolizumab dose may be added, to keep the overall pattern, within the second and third blocks. If a complete response is identified (including after block 1), then pembrolizumab can be continued as specified to the end of block 4, or stopped sooner after at least 2 interval scans showing complete response, at the discretion of the treating physician or the study PI. The protocol specified treatment finishes after the end of the 4th block. This will typically be 36 weeks after start, but extra 3-week cycles of pembrolizumab are allowed, if needed to maintain the overall schedule, so duration of treatment may turn out to be a month or two longer.

There is no dose escalation portion: The dose and schedule of IL-2 is fixed, 600,000 IU/kg/dose, with a cap of 66 mIU/dose. Doses may be omitted for safety. The dose of pembrolizumab is fixed, flat dose 200 mg/dose.

Safety monitoring: Sequential boundaries will be used to monitor dose-limiting toxicity rate. There is a detailed plan in section 8.5

2.3 Pembrolizumab dose plan

Note: The definitions of immune related adverse events (irAE) are 7.1.2.1.

The dose of pembrolizumab is 200 mg/dose. This is an immunotherapy for which a sharp dose-response relationship of the irAEs to the pembrolizumab is not anticipated.

The pembrolizumab dose of subjects already on treatment may be delayed or omitted for safety reasons.

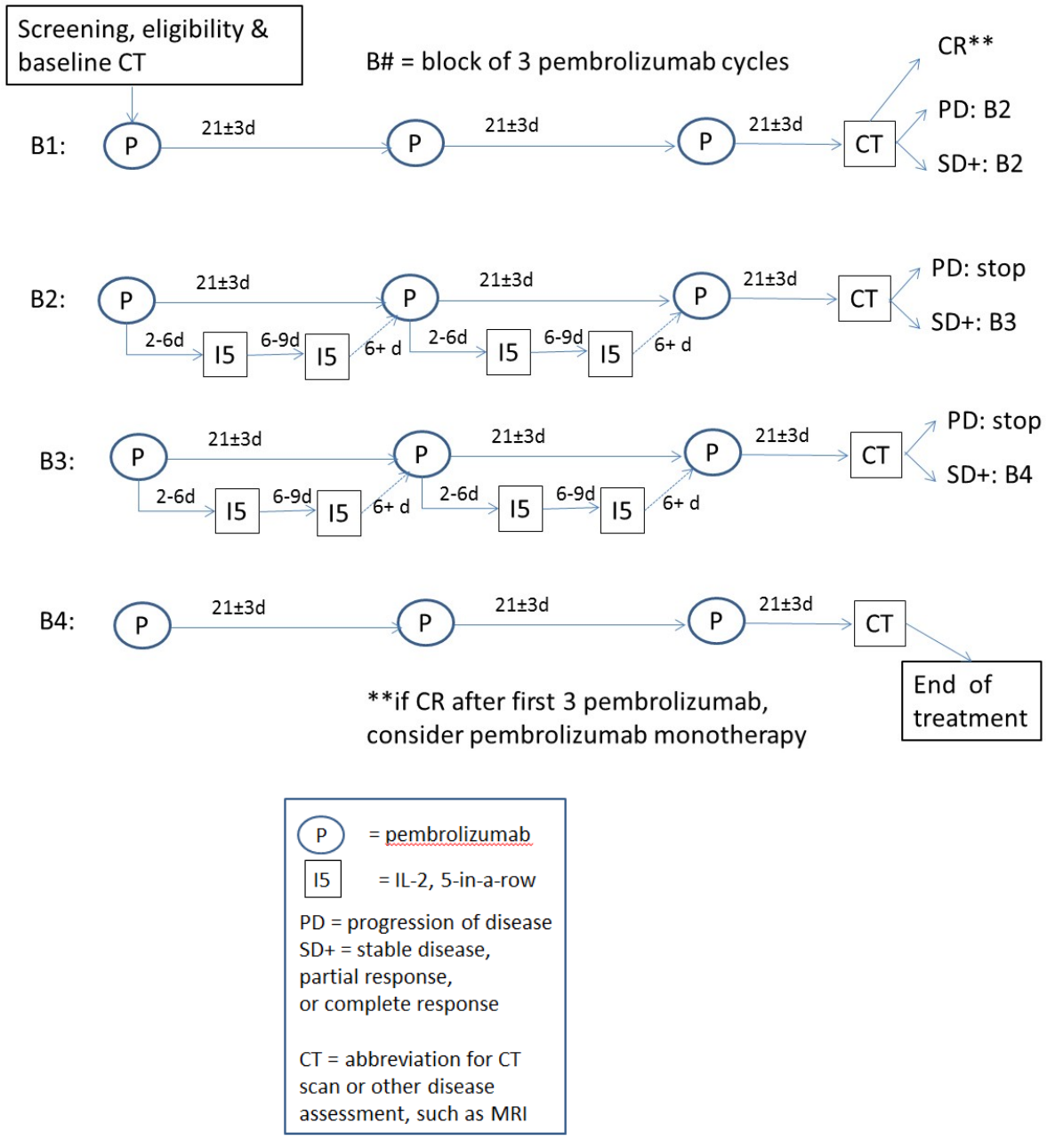
2.4 Trial Diagrams

2.4.1 Treatment intervals

Key features: In the absence of schedule adjustments, all treatment starts (pembrolizumab or IL-2 admission) could be the same day of the week.

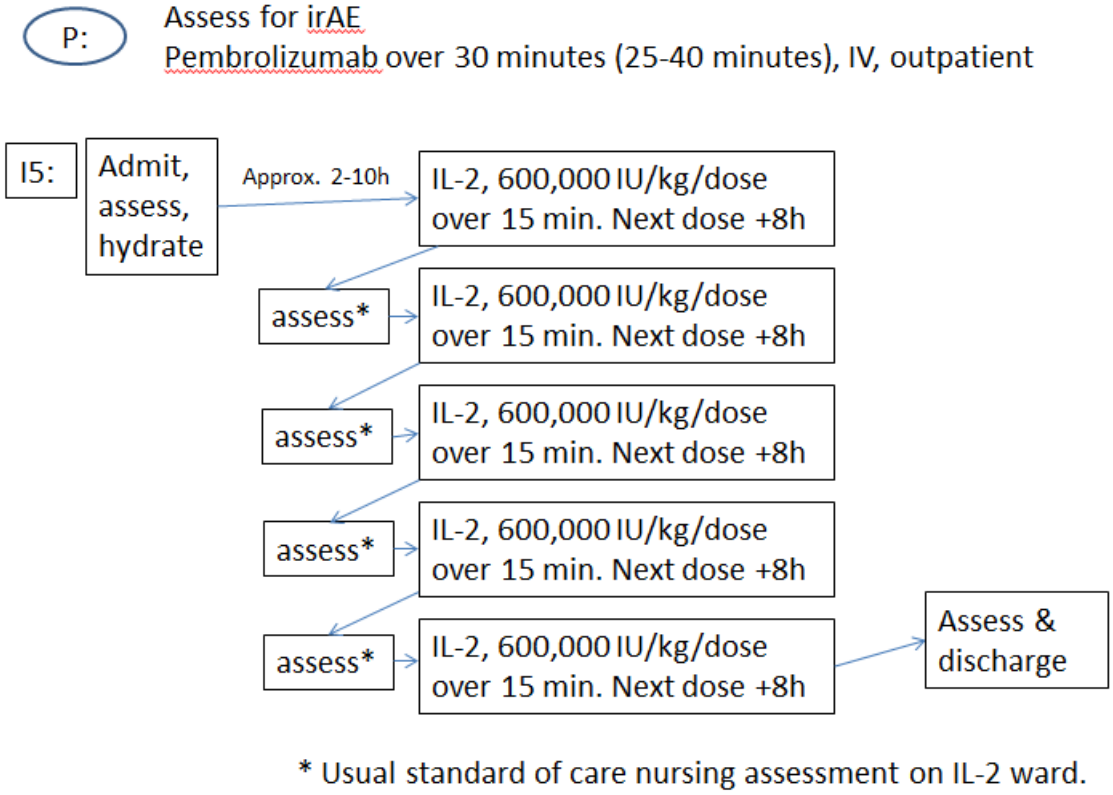
At least 5 days between the end of IL-2 admission and next pembrolizumab infusion gives time for resolution of IL-2 side effects before the irAE assessment before the next pembrolizumab dose.

FIGURE 2: DOSE DAYS INTERVAL DIAGRAM



2.4.2 Infusion intervals

FIGURE 3: INFUSION TIMES AND INTERVALS SUMMARY



3.1 OBJECTIVES & HYPOTHESES

3.2 Primary Objective & Hypothesis

(1) **Objective-Efficacy portion:** Estimate the frequencies of disease response so as to be a basis to commit to more development of this schedule. Note that this is framed broadly, with the understanding that the decision to commit to further development of the schedule includes a variety of feasibility endpoints.

The ORR will be defined as the CR + PR patients, with confirmation of the response status (numerator), among those ever treated (denominator). **Hypothesis:** For the efficacy portion H_0: ORR is <20% and H_A: ORR is>45%. Thus, a 45% ORR (CR + PR) would be considered of definite interest for further development, contingent on the feasibility assessment as well, as part of the decision. With a Simon 2-stage design, 24 evaluable patients are needed.

Objective –Safety portion: The co-primary endpoint of adverse event and serious adverse event tabulation comprises a critical portion of the ultimate assessment of feasibility for moving forward with additional and directly comparative trials using this regimen. There are known frequencies of these (referencing the respective monotherapy prescribing information documents) for which this tabulation can be compared. The relatively small sample size of this series versus those series typically would prevent specific hypothesis testing.

3.3 Secondary Objectives & Hypotheses

(1) **Objective**: ORR for patients getting at least 4 doses of pembrolizumab and one dose of IL-2:

(2) Objective: ORR for, and for patients completing at least 6 doses of pembrolizumab and at least 20 doses of IL-2 (designated as “completing at least half of the treatment per-protocol”.)

(3) **Objective**: This is an exploratory safety objective: OS will be not demonstrably inferior to contemporary subjects with matched clinical risk features from PROCLAIM database observed OS (using $p \geq .05$)

Hypothesis: H_0: OS[1-year] is more than 20% lower than matched controls
H_A: ORR is same or better (using $p \geq .05$)

3.4 Exploratory Objectives

These objectives are expected to be developed as part of testing in parallel with testing of patients on other trials. While the specific conceptual goals are outlined here, the specific tests are not prespecified.

(1) **Objective**: Exploratory analyses dividing retrospectively designated best responders versus remaining patients with respect to a variety of cell subsets, for example: DC:MDSC ratio; CD4+ : CD4: FoxP3+ ratio. CD8+ : NK cell ratio.

Hypothesis: Pretreatment leukocyte characteristics will predict response

(2) **Objective:** Exploratory analyses dividing retrospectively designated best responders versus remaining patients with respect to sets of immune related proteins assayed by Nanostring™ testing of tumor specimens for gene sets that have been proposed to be related to the chance of anticancer immune response.

Hypothesis: The good-responder patients will have an overall pattern consistent with those seen patients with other diagnoses who had had good response after other PD-1 treatment. For example, better responses if there is tissue PD-L1 expression > 5%, or interferon-gamma related gene expression.

(3) **Objective:** Exploratory analyses of selected serum proteins to analyze for markers of immune response.

Hypothesis: The good-responder patients will have an overall pattern consistent with those seen patients with other diagnoses who had had good response after other PD-1 treatment.

4.1 BACKGROUND & RATIONALE

4.2 Background –pembrolizumab (MK-3475)

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

4.2.1 Pharmaceutical and Therapeutic Background

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

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

levels of this T-cell inhibitor. PD-1 has been suggested to regulate tumor-specific T-cell expansion in subjects with melanoma (MEL). This suggests that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and should be considered as an attractive target for therapeutic intervention.

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

4.2.2 Preclinical and Clinical Trial Data

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

4.2 Kidney cancer background

4.2.1 Clear cell renal carcinoma

In 2015 in the US, an estimated 61,560 new cases of renal cell cancer and 14,080 deaths were predicted (National Cancer Institute website 2015. Approximately 85% of renal cancers are adenocarcinomas, which may be classified as clear cell, with a subset of granular cell. The majority of patients are diagnosed when the tumor is still relatively localized. Renal cell carcinoma can be cured if it is diagnosed and treated at this early stage, and overall approximately 40% of patients survive for 5 years. However, for those patients with advanced, recurrent or metastatic disease prognosis is much poorer, and almost all Stage IV tumors are incurable. Of interest, renal cell carcinoma is one of the few tumors in which rare, but well-documented cases of spontaneous regression occur without treatment.

Treatment for Stage IV renal cell carcinoma may include surgical resection of the primary tumor, or of localized metastatic disease, or other localized therapies in selected patients. Cytotoxic chemotherapy shows little benefit but cytokine therapy with interferon alpha or interleukin-2 (IL-2) induces an overall response rate of approximately 15%. High dose IL-2 alone produces durable complete remissions in approximately 5% of patients (Rosenberg 1987, Fisher 1988, Weiss 1992, Rosenberg 1994, Fyfe 1995, McDermott 2005).

Advances in the understanding of the biology of cancer have led to the development and regulatory approval of 6 new drugs since 2005 which target specific growth pathways. Most clear cell renal cell carcinomas carry the Von–Hippel Lindau (VHL) mutation which results in the constitutive production of angiogenesis factors (Schraml 2002), and several recently approved anti-angiogenic targeted drugs have been shown to delay progression in renal cell carcinoma. Axitinib, a highly selective and potent inhibitor of VEGF receptors 1, 2 and 3, is

the most recently approved drug specifically for the treatment of advanced renal cell carcinoma after the failure of one prior systemic therapy.

In addition to primary effects on tumor angiogenesis through the VEGF-signaling axis, there is increasing evidence that these targeted drugs may also elicit anti-tumor effects via complex interactions with the immune system. For example, sunitinib has been shown to reduce recruitment of myeloid-derived suppressor cells (MDSC) and tumor infiltrating Tregs to the tumor site, resulting in augmentation of the anti-tumor response. Renal carcinoma patients treated with sunitinib have improved peripheral blood Type 1 T cell responses (increased gamma interferon and decreased IL-4 production) and also a decrease in circulating Tregs. Increased peritumoral Tregs are a factor associated with poorer overall survival (Finke 2008, Xin 2009). If used in combination with a strong immune-enhancer such as IL-2, the anti-immunosuppression effects of targeted therapies may therefore have a synergistic anti-tumor growth effect.

4.3 Aldesleukin IL-2 background

Use of IL-2 to treat kidney cancer has been an on-label standard of care for over 20 years, with the particular distinction that there is a consistent observation of a core of durable complete responders. That core has been a low percentage; while the durability has been excellent among the responders, and even those who do not have complete response appear to have survival better than the overall population of kidney cancer patients, the key challenge is to get complete responses for more patients.

Another challenge with IL-2 treatment is drug delivery schedule. At least a dozen schedules have ranged from the high dose bolus (600,000 or 720,000) IU/kg/dose for a series of 14 doses (current product label), 600,000 IU/kg/dose on a 5-in-a-row schedule (the one this trial is based on; Yang 2003; McDermott 2005), decrescendo high dose schedule (Lewis 2008), 18 mIU/m2/24 hours x 120 hours continuous infusion (Negrier 1998), 5 mIU/m2/24 hours (Koulova 2005) bolus dosing at 72,000 IU/kg/dose (Yang 1994), and many subcutaneous regimens, such as 250,000 IU/kg/dose for 5 doses and then 125,000 IU/kg/dose for 25 doses at 5 doses per week (Sleijfer, 1992), some integrating interferon alpha (e.g. Atzpodien 1990) and GM-CSF, and other complementary immunomodulatory modalities (e.g. Antonia 2002; Nefedova 2007).

What is missing to make the frequency of complete response higher? The issue of an unmaintained durable complete response has largely eluded the experience of VEGF and mTOR targeted pathway drugs, although they are the main treatments that most of the patients with kidney cancer are getting. That is not to say that the benefit of the targeted drugs is not real; objective tumor regression and impacts on survival are real, just mostly different from the experience of durable, complete response.

Checkpoint inhibitor therapies are inducing some instances of complete response in an unprecedented range of cancers of different histologic types, a big contrast with the prior experience of IL2 that was largely limited to clear cell kidney cancer and melanoma. Observed major responses of checkpoint inhibitor after prior cytokine therapy was observed in early nivolumab experiences, and also in later kidney cancer specific trials, and in a case report the converse sequence showed that IL-2 induced complete response after no regression on nivolumab. PDL1 expression in RCC has been suggested as a possible predictor of better response to IL-2 (Bailey 2103).

The tumor attributes that are permissive for an effective complete response to occur remain to be studied and decoded. Ultimately, this project and others will be a part of this scientific discovery process; the answers will be complex, not simple single protein or cell type classifications.

4.4 Rationale for the Trial and Selected Subject Population

4.4.1 Rationale for Pembrolizumab Dose Selection

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

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

A population pharmacokinetic analysis has been performed using serum concentration time data from 476 patients. Within the resulting population PK model, clearance and volume parameters of MK-3475 were found to be dependent on body weight. The relationship

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

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

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

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

4.4.2 Rationale for the 5-in-a row IL-2 Schedule

A variety of IL-2 schedules have been tested in the clinical development. An incomplete list demonstrating the spectrum of these include the on-label dose, 14 consecutive doses, at 15 minute infusion, of 600,000 or 720,000 IU/kg/dose for the first course, and then a second course 9-16 days later, with each series of 14 being ended by a composite ending criterion

rule including creatinine elevation, transaminitis, hyperbilirubinemia, peripheral edema, dyspnea, oliguria, tachycardia, hypotension, fatigue, or other clinical defined stopping issue. Others which have been formally tested include low doses given intravenously (72,000 IU/kg/dose) on about the same schedule; continuous intravenous infusion (18 million IU/kg/24 hours x 120hours); subcutaneous schedules such as 250,000 IU/kg/dose, daily for 5 days in week 1 then 125,000 IU/kg/dose for 5 daily doses in weeks 2-6; concurrent with TIL (tumor infiltrating lymphocyte) administration on a high dose schedule, and decrescendo schedule, and with concurrent chemotherapy (biochemotherapy) and with concurrent interferon.

Of note, the on-label dose was the superior arm in two separate phase III randomized studies that compared that dose to either low-dose subcutaneous interferon and interleukin-2, or to low-dose interleukin-2 monotherapy.

On a biological basis, two main populations of IL-2 receptors are present: The low-affinity receptor, with IL-2Rβ and IL-2Rγ (CD 122 and CD132) only, and the high affinity receptor with IL2-Rα (CD25) IL-2Rβ and IL-2Rγ. While either are ligated during the high dose administration, only the latter have high activation during low dose administration. It is the former, low affinity receptors, that may be the drivers of the functional anticancer lymphocyte effectors of kidney cancer clearance. Whether the NK cells, or CD8 T cells are either exclusively the relevant effector subset is not demonstrably established, despite decades of study.

The 5-in-a-row schedule to be developed further here was the subject of a single-arm trial at Moffitt Cancer Center. The maintenance of the high dose, bolus format was selected to maintain the same biologic level of receptor ligation as on a standard schedule. A typical dose-delivery on the on-label 14-in-a-row schedule is 8-10 doses, or for two courses, about 20 doses. The nominal total of 28/28 doses has been seldom attained. By splitting the total IL-2 of the IL-2 doses into four parts, of 5 planned doses each, a few favorable features are obtained: Each run of IL-2 is usually completed, or if not, the severity of the course-limiting event is less extreme. Most practically, the need to transfer patient to intensive care unit monitoring could be less frequent, and that will contribute substantially to perception of feasibility of the treatment. The total overall dose delivery is maintained. There are 3 natural breaks between the four courses, instead of just one, and this accommodates adjustment of intervals between doses as needed for side effects management. Additionally, since each hospitalization is for 3 days, the start and finish can be defined with more certainty, helpful for planning admissions, and helpful for the patient's psychological outlook on the duration of each inpatient block

In that pilot study, among 20 kidney cancer patients, 5 had major responses (two complete), and median overall survival was not reached at 5 years. (Finkelstein 2010) 16 melanoma

patients were also treated on that study. While a single arm study of the that protocol's size cannot typically be mathematically definitive as comparative basis for the relative efficacy of the standard schedule, it does at least appear not worse than the 7%-8% CR rate and 21-23% ORR and ~17-24 months median survival described in the phase III clinical trials that used high dose IL-2 bolus (14-in-a-row) therapy as one arm (Yang 2003; McDermott 2005), or the phase III trial with continuous infusion (18 months; Negrier 1998). Those trials were in the pre-VEGFR-TKI era; contemporary risk stratification additionally makes a direct comparison prohibitive. Prior IL-2 therapy and then progression and then axitinib was described to show median overall survival of 30 months (Rixe 2007); the contemporary experience of IL-2 then targeted therapy is the subject of pending analysis through the PROCLAIM registry. Finally, the total cumulative dose administration, per course, is maintained, with most of the subjects in the pilot study getting 18-20 doses, out of the 20 planned.

The aspect of the 14-in-a-row IL-2 schedule which is concurrently a subjective barrier for patient and physician acceptance and more frequent application, and also a barrier for IL-2 combination therapy development is the use of runs of IL-2 treatment courses that consistently end with a limiting problem within the composite endpoint as described: hypotension, oliguria, malaise and others. These present an almost guaranteed high-grade side effect exposure, and this can be anticipated to obfuscate the relative contribution to acute side effects of a putative partner drug. This defines another theoretical advantage that is a rationale for selection of the 5-in-a-row IL-2 schedule for use in this trial.

4.4.3 Rationale for RCC subtypes

Most kidney cancer drug development has been either on an open histology basis – using the anatomic site of origin to restrict patients, mostly in older studies, or limited to clear cell type kidney cancer, in most newer studies. With retrospectively observed IL-2 complete responses mainly in clear cell RCC subtypes, and recognizing that the reference group for response assessments will be clear cell RCC patients treated with IL-2, at a practical level most of the patients should be clear cell RCC.

Since part of the study hypothesis is that the anticancer activity of these drugs together will be better than either alone, and the feasibility of the regimen is a primary endpoint, a few patients that are not clear cell type could be allowed in the cohort. Initially, however, to maintain a study population that is comparable to prior experiences, only clear cell type will be included. Future development need not continue that restriction.

4.4.4 Rationale for Endpoints

4.4.4.1 Efficacy & Dose Delivery Endpoints

This is primarily a feasibility study. There is a formal safety format, because this is the initial human clinical experience with the two drugs together on this schedule. Feasibility for further development encompasses two issues:

The first is the response rate of the disease. The trial design is a small, single arm design and would not be definitive for a registration or practice changing decision. Thus, the response rate will not be determined with high precision. Since differentiation of CR and very-good PR, by radiologic criteria, can be an issue for which determinations are ambiguous, and since the CR+PR (major response rate) is the typical metric for a new combination evaluation, the CR will be assessed, but the CR+ PR will be used as the primary outcome measure. Another key metric is overall survival or progression free survival; these have been shown to be typically better among patients who have been treated with IL-2 than those (non-randomly assigned) to not get IL-2, but require much longer time frame for follow up, and again do not lend themselves to definitive analysis in the present single arm trial.

The second is the dose delivery. The proposition of this trial is that each of the drugs will contribute, and that this schedule is relevant. That can only be part of the logical conclusion if patients actually get the treatments as planned. If a very low dose delivery is achieved, and a high response rate is observed – that is generally good, but favors planning to use a different schedule in further testing. If a high dose delivery is achieved, but the response rate is unfavorable, that technically meets feasibility, but does not favor planning to continue to use this schedule. If the overall response rate (primary endpoint) of the trial is met and the dose delivery is relatively good, that would favor continued development of this dose and schedule for these drugs, for these type of patients.

Rationale for assessment of the fraction of patients with at least half the doses

In the randomized study of nivolumab versus everolimus, the median progression free survival was 4.6 months, corresponding to what would be about 6.5 blocks of 21 days. Thus, 6 pembrolizumab doses is of interest, because it corresponds to a duration of PD-1 inhibition for which an overall survival benefit was demonstrated in patients with metastatic clear cell renal cancer. The total number of pembrolizumab doses planned in this study is 12. Six doses, whether all in a row, or in the unusual circumstance of interruption and then later administration, would be a cumulative dose of interest for that reason. (Motzer 2015)

The total number of doses needed to have an IL-2 response is not firmly defined, despite decades of study. In the randomized study of high dose IL-2 vs low dose IL-2 and interferon, for which a statistically superior overall survival difference was observed in the former arm,

the dose delivery of 68% of 28 doses, that is 19 doses was used, for cycle #1. Later cycles were not summarized, the majority of patients did not get later cycles. (McDermott 2015) In the 2016 ASCO meeting, a threshold of at least 18 high dose IL-2 doses was identified as a marker of better response outcomes (Chow et al. 2016)

Thus 6 doses of pembrolizumab covers about the same dose duration of nivolumab, and 20 doses of IL-2 define threshold levels of drug delivery for which survival impact has been demonstrated in phase III randomized immunotherapy trials in patients with metastatic clear cell kidney cancer. The patients in those trials are not anticipated to be a group of patients which can be directly compared to the patients in this trial, because of the shifting availability other drugs, and contemporary patient selection. (Motzer 2015)

For this purpose, a prospective definition of a achieving a minimal dose delivery will be set as at least 6 pembrolizumab doses and at least 20 IL-2 doses. Each patient will be assessed for this, not the overall averages. Other definitions can be considered; this feasibility concept is one that is used in conjunction with the efficacy part of the primary objective, the ORR estimate.

4.4.4.2 Biomarker Research

Biomarkers of the capacity for anticancer response are an important objective across the field of immunotherapy.

Specimen collection at 4 time points will accommodate testing in coordination with other data sets. The plan will include:

FIGURE 4: TYPES AND TIMES OF CORRELATIVE SPECIMENS

Baseline (pretreatment or B1D1)	Archival tumor Leukocytes Serum
After 4 doses pembrolizumab/before IL-2 (B2W2)	Leukocytes Serum
After 10x IL-2	Leukocytes

(B2W4)	Serum
After all IL-2 (B4W1)	Leukocytes Serum

4.5 Combination rationale

IL-2 and kidney cancer: The susceptibility of kidney cancer to IL-2 treatment has been a cornerstone of the cancer immunotherapy, but with limitations that define a ceiling on its overall the kidney cancer and generalizable oncologic impacts. Dimensions of this are limitations on how frequently complete responses are observed, and how many patients can tolerate a standard schedule, and how to build on (the current label) standard schedule, and how to have more centers available to patients. On the other hand, the achievement of unmaintained durable responses at 10-20+ years is not a limitation, but an opportunity and a standard for other anticancer therapies to aspire. The standard high-dose IL-2 inpatient treatment has associated high frequency side effects that must be managed in an experienced setting; not necessarily severe or debilitating, but requiring a base of experience for hospital staff and physician. Building on over 20 years' experience, many functional IL-2 administration centers with a steady (narrow) stream of patients having IL-2 administration and responses. These are tabulated in the Prometheus sponsored PROCLAIM registry (Wong et al. *J Immunother Cancer.* 2014; 2: 20). As practical issues of immunotherapy response determinants are developed, driven by responses and durable responses, a wider use of immunotherapy – cell therapies, checkpoints, or cytokines – can be anticipated.

Checkpoint inhibition and kidney cancer: Cancer immunotherapy with checkpoint inhibitors has demonstrated potential for clinical impact in many cancers, including in kidney cancer. With regard to clinical experiences in PD-1 inhibition, trials with nivolumab monotherapy (Choueiri ASCO 2014 #5012), and with ipilimumab + nivolumab (Hammers ASCO 2014 #4504) are examples of patients with kidney cancer with observed major regression after treatment including PD-1 checkpoint inhibition without other therapies. VEGF + checkpoint inhibition. Our case report observation of RCC regression on IL-2 after prior nonresponse to nivolumab (Brayer 2014) is a pointed example that immunotherapy responses to different drugs do not all represent responses within the same small subset of patients. Use of more, different immunotherapies may be a way to on a bigger fraction of the incident patient population. Registrational size phase III studies of nivolumab after VEGFR-TKI progression and of iplimumab + nivolumab as initial therapy are ongoing, with trial hypotheses to impact on median (50^{th} percentile) survival. The relative potential of pembroluzimab vs other PD-1 pathway antibody drugs such as nivolumab, MEDI-4376, MPLD3280a, particularly in

patients with tumors that bear markers of immune susceptibility (such as lymphocytic infiltrates, or 12-chemokine signature, or PD-L1 expression) remains to be developed for kidney cancer therapy. Combination therapies overlapping checkpoint inhibition with VEGF treatments, just in kidney cancer, include axitinib and pembrolizumab (open at Moffitt), as well as nivolumab, and ipilmimab. Many other disease states are under study, including with approved VEGF pathway drugs.

Checkpoints and cytokines, together: Every lymphocyte that is an effector of checkpoint inhibition response has IL-2 receptor on it (NK cells, T cells, B-cells all have IL-2 receptors). Conversely, every IL-2 activated lymphocyte, whether bearing low & intermediate affinity receptor (CD25 [IL2Rα] or CD 122 & 132 [IL2Rβ & IL2Rɣ]) or high affinity receptor (CD25, CD122, CD132) has potential to have been modulated by PD-1 pathway, or to be later affected either directly through its own PD-1 receptors, or indirectly through the changed behavior of other lymphocytes bearing PD-1 receptor. As described by in our recent AACR poster (Choueiri *et al* 2014) PD-1 inhibition in kidney cancer patients induces two changes that are encouraging for synergy – more intratumoral lymphocytes, and more IL-2 receptor (βchain).

The core common feature of these immune therapies is that the lymphocytes bear receptors of both of these drugs and the intratumoral resistance mechanisms remain to be completely defined. One common feature, for example, may be that tumors with no discernable penetration by leukocytes are resistant. Another may be that patients with a high burden of tolerance promoting myeloid derived suppressor cells will not reach a response. How will NK and T cells respond to IL-2 in the context of PD-1 inhibition? That is the central biological question. That biological question is fundamental to the key clinical questions: Will more tumors regress? Will immunologic side effects be amplified in the short term? Will immunologic side effects be amplified in the long term? Both drugs have limitations—IL-2 with short term toxicity, pembrolizumab with unestablished durability of responses, potential for late autoimmune toxicity, and both with limited overall response frequency and incomplete algorithms for patient selection. However, this study will work towards finding a regimen that is feasible, and ultimately raising rates of durable, unmaintained remissions the central goal of oncolytic therapeutics.

The rationale for the pembroluzimab and IL-2 combination in this study is to achieve safely a cooperative anticancer effect of both drugs. This is to use high dose, bolus IL-2 (so as to still have ligation of low affinity IL-2R), on a schedule that we had developed to accommodate having a relatively more stable overall dose delivery (5-in-a-row doses x four 3-day admissions instead of 14-in-a-row with two 6 day admissions; Finkelstein 2010), on a schedule that is reliable, and usually ends each course without a critical IL-2 dosing limitation. This now will be done in a context of inhibition of PD-1. This development will

have to be done in a measured way, using experienced centers because of the unknowns as far as possible exacerbations of immune-related side effects. If response frequency and dose delivery appear promising, multicenter development will be appealing. In a small series such as this, the potential of each drug to induce a completer response in some patients is acknowledged – this is totally consistent with the rationale of combining these two for the central oncologic goal of increasing the fraction of complete responses. The scope of this study is limited to establishing this a as feasible schedule. Efficacy can be measured as progression free survival, major response rate, complete response rate, landmark 1-year survival, or median overall survival, any of which could be fundamental and reasonable components for the rational further development of oncologic therapeutics.

Pharmacodynamic testing of lymphocytes should recapitulate the experiences of the nivolumab RCC treatment trial, as far as altered expression of lymphocytes proteins, and may define a way to understand the processes underlying clinical resistance, to be tested in further future trials.

5.1 METHODOLOGY

5.2 Entry Criteria

5.2.1 Diagnosis/Condition for Entry into the Trial

Metastatic kidney cancer. Clear cell histology component from primary or metastatic lesion.

5.2.2 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. Age over 18 on day of signing informed consent.
3. Have measurable disease based on RECIST 1.1.

   http://ctep.cancer.gov/protocolDevelopment/docs/Recist_Guideline.pdf
4. Be willing to provide tissue from a newly obtained or archival tissue, if available.
5. Have a performance status of 0 or 1 on the ECOG Performance Scale.
6. Demonstrate adequate organ function as defined in Table 1.

Table 1 Adequate Organ Function Laboratory Values

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

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

8. Female subjects of childbearing potential must agree to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of study medication (Reference Section 5.8.2). Subjects of childbearing potential are those who have not been surgically sterilized or have not been free from menses for > 1 year.

9. Male subjects must 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.

10. Cardiac testing with either exercise stress test or thallium stress test, within 3 months of start of the first treatment day. Atrial fibrillation that is rate controlled is allowed. Note – the first treatment day is about 9 weeks before the first IL-2 treatment day. If a cardiologist's evaluation determines that this is superfluous based on other assessments, then this may be omitted.

11. Pulmonary function test is required, within 3 months of start. The treating physician will assess suitability by usual clinical criteria used for IL-2 treatment generally

consistent with the Proleukin™ prescribing information. There is no specific minimum result specified by the procotol

5.2.3 Subject Exclusion Criteria

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

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

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

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

4. Has hypersensitivity to pembrolizumab or any of its excipients.

5. The number of prior therapies is restricted as follows:

Zero or one prior therapies during the preceding one year. This serves to limit the treatment cohort to patients with either only slowly progressive disease, or up to one prior therapy.

No prior PD-1 or PD-L1 antibody therapies are allowed, as in #16

Prior IL-2 is allowed, if it finished more than 1 year prior.

The following are not counted as medical therapies: nephrectomy, radiation therapy, other energy-ablative techniques, or metastasectomy.

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

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

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

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

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

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

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

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

12. Has an active infection requiring systemic therapy.

13. 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.

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

15. 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.

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

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

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

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

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

20. Myocardial infarction, stroke, coronary artery bypass surgery, coronary stent, or unstable angina within one year are excluded.

Note: A subject may enroll in the study and have a start date set in the near future in a way that meets the timelines for exclusion items by the treatment start date

5.2 Trial Treatments

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 outpatient	Every 21d ± 3d	Experimental
Interleukin-2	15 minute infusion of 600,000 IU/kg/dose*	q8h x5	IV infusion over 15 minutes, inpatient	Two courses set after corresponding pembrolizumab that defines day 1 of the cycle with intervals of: P→ W1: 2-9 days, usually 7 days W1→ W2: 6-9 days usually 7 days	Standard
*actual body weight; capped at 66 million IU/dose for subjects > 110 kg. P = date of pembrolizumab dose W1 = date of first IL-2 dose of the course W2 = date of first IL-2 dose of the next course					

Trial treatment should begin as close as practical to the date on which eligibility is established and treatment level is allocated (for those patients on the part of the trial where the pembrolizumab dose is still not fixed).

5.2.1 Dose Selection/Modification

5.2.1.1 Dose Selection

The rationale for selection of the 200 mg/dose flat dose to be used in this trial is provided in Section 4.0 – Background and Rationale.

Details on preparation and administration of pembrolizumab (MK-3475) are provided in the Pharmacy Manual.

5.2.1.2 Dose Modification

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 pembrolizumab-related toxicities and severe or life-threatening AEs as per Table 3 below. See Section 5.6.1 and Events of Clinical Interest Guidance Document for supportive care guidelines, including use of corticosteroids.

In general, dose modifications of pembrolizumab are not required for events that appear to be directly related to interleukin-2 treatment and have resolved to a grade that is assessed as safe by the principle investigator, at the time of the next planned pembrolizumab treatment.

Table 3

Dose Modification Guidelines for Drug-Related Adverse Events

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

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

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

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

Dosing interruptions are permitted in the case of medical / surgical events or logistical reasons not related to study therapy (e.g., elective surgery, unrelated medical events, patient vacation, and/or holidays). Subjects should be placed back on study therapy within 3 weeks

of the scheduled interruption, unless otherwise discussed with the Sponsor. The reason for interruption should be documented in the patient's study record.

Note: These evaluations should be done in relation to each pembrolizumab dose. Adverse events that occur or are noted in between scheduled pembrolizumab infusions, but are within 2 weeks after IL-2 administration and appear to meet Table 3 criteria, and have resolved at the point of the next pembrolizumab dose, and are attributed to the IL-2 treatment's acute side effects do not count as events that are required to be managed as indicated in Table 3. For example, grade 3 creatinine elevation that resolved after the IL-2 was finished but before the next pembrolizumab infusion would not count as an AE that requires interruption of the pembrolizumab treatment schedule.

5.2.2 Timing of Dose Administration

Trial pembrolizumab treatment should be administered on Day 1 of each 3 week pembrolizumab cycle after all procedures or assessments have been completed as detailed on the Trial Flow Chart (Section 6.0), within the specified window. Trial treatment may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative or other practical reasons.

Pembrolizumab 200 mg target infusion time is to be 30 minutes However, given the variability of infusion pumps, a window of -5 minutes and +10 minutes is permitted (*i.e.*, infusion time is 30 minutes: -5 min/+10 min, which is 25 to 40 minutes).

The Pharmacy Manual contains specific instructions for the preparation of the pembrolizumab infusion fluid and administration of infusion solution.

Terminology notes:

To keep with most of the pembrolizumab development, one "cycle" is designated as a 3 week span of time with one dose of pembrolizumab on the first day. To avoid confusion, for this document, the term "cycle" will be avoided for the IL-2 treatment courses, or for the time in between CT scans.

One "block" for protocol purposes is a group of three (or four) pembrolizumab cycles. The pembrolizumab cycles are numbered a #1, #2, and #3. A fourth cycle will be designated as #4e", where "e" means extra, for an extra pembrolizumab-only 3-week cycle added to accommodate *any* scheduling issues.

There are eight hospital admissions for IL-2 treatment, which are in the second and third weeks on the first and second cycles of the second and third blocks. These will be designated by the approximate week within the block, using B2 for the second block and B3 for the third block, and thus, for B2: B2W2, B2W3, B2W5, B2W6, and correspondingly for B3W2, B3W3, B3W5 & B3W6.

Since the "week" designation can be affected by intervals that are permissible (such as 6 days, that would technically be during the same (*conventional definition*) calendar week, the protocol document will avoid designating the IL2 doses a being scheduled within a particular "week", but instead will use the abbreviations defined above. (B2W2, etc.) where possible.

This is the whole schedule:

Start of block B1:

Cycle 1 pembrolizumab dose 1. Interval to next dose 21 ± 3 days.

Cycle 2 pembrolizumab dose 2. Interval to next dose 21 ±3 days.

Cycle 3 pembrolizumab dose 3. Interval to next dose 21 ±3 days.

End of block 1: 21 days after third pembrolizumab dose, or first pembrolizumab dose of next cycle, or 87 days after start. (This accommodates possible insertion of a "#4e" extra cycle of pembrolizumab, if needed).

Start of block B2:

Cycle 1 pembrolizumab dose 1. Interval to next dose 21 ±3 days.

IL2 admission designated as "B2W2": Usually 7 days, but target 2-9 days after block 2 cycle 1 pembrolizumab.

IL2 admission designated as "B2W3": Usually 7 days, but target 6-9 days after B2W2.

Cycle 2 pembrolizumab dose 2. At least 3 days but usually 7 days, or up to 10 days after B2W3. Interval to next pembrolizumab dose 21 ±3 days.

IL2 admission designated as "B2W5": Usually 7 days, but target 2-9 days after block 2 cycle 2 pembrolizumab.

IL2 admission designated as "B2W6": Usually 7 days, but target 6-9 days after B2W5.

Cycle 3 pembrolizumab dose 3. Interval to next dose 21 ± 3 days.

End of block B2: 21 days after third pembrolizumab dose, or first pembrolizumab dose of next cycle, or 87 days after start of the first pembrolizumab dose of the block (If "#4e" used.)

Start of block B3:

Cycle 1 pembrolizumab dose 1. Interval to next dose 21 ±3 days.

IL2 admission designated as"B3W2": Usually 7 days, but target 2-9 days after block 2 cycle 1 pembrolizumab.

IL2 admission designated as "B3W3": Usually 7 days, but target 6-9 days after B3W2.

Cycle 2 pembrolizumab dose 2. At least 3 days but usually 7 days, or up to 10 days after B2W3. Interval to next pembrolizumab dose 21 ±3 days.

IL2 admission designated as "B3W5": Usually 7 days, but target 2-9 days after block 2 cycle 2 pembrolizumab.

IL2 admission designated as "B3W6": Usually 7 days, but target 6-9 days after B3W5.

Cycle 3 pembrolizumab dose 3. Interval to next dose 21 ±3 days.

End of cycle 3: 21 days after third pembrolizumab dose, or first pembrolizumab dose of next cycle, or 87 days after start of the first pembrolizumab dose of the block. (If cycle #4e is used.)

Start of block B4:

Cycle 1 pembrolizumab dose 1. Interval to next dose 21 ±3 days.

Cycle 2 pembrolizumab dose 2. Interval to next dose 21 ±3 days.

Cycle 3 pembrolizumab dose 3. Interval to next dose 21 ±3 days.

End of block 4: 21 days after third pembrolizumab dose. A cycle #4e may be used if a scan delay is anticipated. The end of block 4 is the end of the treatment phase of the study.

5.2.3 No Trial Blinding

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

5.2.4 IL-2 treatment checklist, before each IL-2 dose.

Note: This list does not supersede the treating physician judgment on whether to withhold a dose or not.

Lab results – refer to most recent results, generally fewer than 28 hours old.

a. No current use of steroids or other anti-immune treatments prescribed for management of autoimmune problems. (Use of glucocorticoids for patients who are hypoadrenal is allowed).
b. No Grade 2 or worse ongoing pembrolizumab-attributed events (Table 6b).
c. Patient willingness to take another IL-2 dose – query nausea, motivation.
d. Not requiring oxygen supplement 2L/min or less for oxygen saturation of 90% or more.
e. Most recent creatinine level should be:
    a. under 150% of baseline value to start a course
    b. under 250% of baseline at most recent evaluation for later doses in the same course. (see note on physician judgment)
f. Systolic blood pressure above target level:
    a. i. Target = 80 mmHg if baseline was <100
    b. ii. Target = 85 mmHg if baseline was 100-120
    c. iii. Target =90 mmHg if baseline was 120+ mmHg systolic
g. If atrial fibrillation is present—treating physician evaluation on per-case basis.
h. Heart rate not documented as continuously 120 for more than 1 hour (during prior 8 hours).
i. Dopamine off, or less than or equal to 2 mcg/kg/min.
j. Urine output > 150 ml over last 8 hours.
k. Two or fewer 500 ml NS bolus had been required in last 8 hours for treating blood pressure or urine output.
l. Electrolytes and liver function tests should be reviewed by treating physician.

5.3 Response assessment and classification

Only patients with measurable disease at baseline should be included because objective tumor response is a part of the primary endpoint. Tumor assessments will be taken at baseline and during a defined window at the end of each *Block* and at 1 year.

5.3.1 Measurable lesions

Measurable Lesions are lesions that can be accurately measured in two perpendicular diameters, with at least one diameter ≥ 20 mm and the other dimension ≥ 10 mm (10 mm x 10 mm for spiral CT). The area will be defined as the product of the largest diameter with its perpendicular

5.3.2 Non-measurable lesions

All other lesions, including unidimensionally measurable disease and small lesions (lesions without at least one diameter ≥ 20 mm), and any of the following:

- Lesions occurring in a previously irradiated area (unless they are documented as new lesions since the completion of radiation therapy), bone lesions, leptomeningeal disease, ascites, pleural or pericardial effusion, lymphangitis cutis/pulmonis, abdominal masses that are not pathologically/cytologically confirmed and followed by imaging techniques and cystic lesions.

All measurable and non-measurable lesions should be measured at screening and at the defined tumor assessment time points. Extra assessments may be performed, as clinically indicated, if there is a suspicion of progression

5.3.3 Immune-related response criteria (irRC)

The irRC are the measurement of overall tumor burden as a metric of disease progression, as compared to the limitation to baseline lesion measurements taken with WHO and RECIST. According to irRC, new lesions do not constitute disease progression if net tumor burden (including new lesions) is stable or decreases. The irRC also permit disease progression prior to response and introduce the concept of confirmation of progression at a subsequent time point after first detection. This accounts for the period required for activated T-cells to infiltrate the tumor, which may cause initial tumor volume increase but can subsequently translate into tumor shrinkage. The irRC also classify durable stable disease as clinical activity. (Wolchok et al., 2009)

Note: irRECIST will be used for the primary response tabulations.

5.3.4 Overall Response According to Immune-related response criteria (irRC)

FIGURE 5: irRC SUMMARY

	irRC
New, measurable lesions (i.e. ≥5 x 5 mm)	Incorporated into tumor burden
New, nonmeasurable lesions (i.e., <5 x 5 mm)	Do not define progression (but preclude irCR)
Non-index lesions	Contribute to defining irCR (complete disappearance required)
Complete Response (CR)	Disappearance of all lesions in two consecutive observation not less than 4 weeks apart
Partial Response (PR)	≥50% decrease in tumor burden compared with baseline in two observations at least 4 weeks apart
Stable Disease (SD)	50% decrease in tumor burden compared with baseline cannot be established nor 25% increase compared with nadir
Progressive Disease (PD)	At least 25% increase in tumor burden compared with nadir (at any single time point) in two consecutive observations at least 4 weeks apart
Near Complete Response (Near CR)	Reduction in tumor by > 90% and no new lesions in two consecutive observations not less than 4 weeks apart.
Unknown (UN):	Assessment of target lesions cannot be made due to insufficient or unevaluable data. In this case, a concise explanation must be given.

Note: If tumor response data is missing for target lesions, the overall assessment must be UN (unknown) unless there is new disease that would result in an overall assessment of PD. However, if there is missing or unevaluable data for non-target lesions, but data is available for all target lesions, the overall response for that time point will be assigned based on the sum LD of all target lesions. Additionally, the assessment of CR cannot be made if there is missing or unevaluable data for non-target lesions. In this case, the overall assessment would be PR.

Definition of New Lesion: Previously unseen lesions >5x5 mm in size will be incorporated into tumor burden.

5.4 Randomization or Treatment Allocation

There is no randomization on this trial.

5.5 Stratification

There is no stratification on this trial, as there is only one arm..

Risk features are tabulated for accommodation of retrospective comparisons of outcomes.

These may include:

1. Age
2. Time from diagnosis to treatment
3. Sites of metastatic disease
4. Absolute neutrophil count
5. Hemoglobin
6. Platelet count
7. LDH
8. Calcium
9. Albumin
10. Nephrectomy status
11. Prior therapy

5.6 Concomitant Medications/Vaccinations (allowed & prohibited)

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

5.6.1 Acceptable Concomitant Medications

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

All concomitant medications received within 28 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded. Concomitant

medications administered after 30 days after the last dose of trial treatment should be recorded for SAEs and ECIs as defined in Section 7.2.

5.6.2 Prohibited Concomitant Medications

Subjects are prohibited from receiving the following therapies during the 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.

Note: A supportive medication or vaccination that has been prospectively approved by the principal investigator, or administered for a medically urgent reason and then later approved by the principal investigator, at a point in time after the patient has met inclusion criteria and before administration of the medication nor vaccination in question, and the patient has started on the first pembrolizumab dose cannot count as a protocol violation for reason of a prohibited concomitant medication violation.

5.7 Rescue Medications & Supportive Care

5.7.1 Supportive Care Guidelines for events attributed to pembrolizumab

Note: Each adverse event will be attributed by the treating physician or the PI as follows:

(1) Likely from pembrolizumab, but not to particularly to IL-2

(2) Likely from IL-2, but not particularly to pembrolizumab

(3) Likely from the combination of IL-2 and pembrolizumab

(4) Not apparently related to either IL-2 nor pembrolizumab.

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

The treatment guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab. The treatment of events that the investigator determines to be related to interleukin-2 may be managed in the usual manner, with no specific restrictions related to the participation in the protocol.

Note: If after the evaluation the event is determined to be not related, the investigator is instructed to follow the ECI reporting guidance but does not need to follow the treatment guidance (as outlined in the ECI guidance document). Refer to Section 5.2.1 for dose modification. For this trial, this particularly pertains to adverse events that are assessed to be usual events as described on the Proleukin™ prescribing information. (www.proleukin.com)

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

- **Pneumonitis**:

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

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

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

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

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

- **Hypophysitis**:

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

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

  - **Grade 2** hyperthyroidism events (and **Grade 2-4** hypothyroidism):
    - In hyperthyroidism, non-selective beta-blockers (e.g. propranolol) are suggested as initial therapy.
    - In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyroinine, is indicated per standard of care.
    - *Note: hyper- and hypothyroidism may occur in relation to IL-2 as well. The discontinuation or continuation of pembrolizumab is at the discretion of the treating physician.*

  - **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.
  - *Note: Isolated elevation of creatinine occurring in relation to IL-2 administration should be evaluated over several days to assess if there is actually a nephritis or not, before committing to use of systemic corticosteroids.*

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

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

Table 4 Infusion Reaction Treatment Guidelines

Note: Every event, such as isolated hypotension or oliguria or elevation of creatinine should be critically evaluated for attribution to IL-2 or to pembrolizumab. Those occurring after IL-2 treatment should be expected to have resolved before the next pembrolizumab infusion, which is at least 6 days later.

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for < =24 hrs	**Stop Infusion and monitor symptoms.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Increase monitoring of vital signs as medically	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab (MK-3475) with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic).

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
	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.**	
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **Subject is permanently discontinued from further trial treatment administration.**	No subsequent dosing
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.		

5.8 Diet/Activity/Other Considerations

5.8.1 Diet

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

5.8.2 Contraception

Pembrolizumab may have adverse effects on a fetus in utero. Furthermore, it is not known if pembrolizumab has transient adverse effects on the composition of sperm. Non-pregnant, non-breast-feeding women may be enrolled if they are willing to use 2 methods of birth control or are considered highly unlikely to conceive. Highly unlikely to conceive is defined as 1) surgically sterilized, or 2) postmenopausal (a woman who is ≥45 years of age and has not had menses for greater than 1 year will be considered postmenopausal), or 3) not heterosexually active for the duration of the study. The two birth control methods can be either two barrier methods or a barrier method plus a hormonal method to prevent pregnancy.

Subjects should start using birth control from study Visit 1 throughout the study period up to 120 days after the last dose of study therapy.

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

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

5.8.3 Use in Pregnancy

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

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

5.8.4 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.

5.9 Subject Withdrawal/Discontinuation Criteria

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

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

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

  Note: For unconfirmed radiographic disease progression, please see Section 5.2.2

  Note: A subject may be granted an exception to continue on treatment with confirmed radiographic progression if clinically stable or clinically improved, please see Section 7.1.2.7.1
- Unacceptable adverse experiences as described in Section 5.2.1.2
- Intercurrent illness that prevents further administration of treatment
- Investigator's decision to withdraw the subject
- The subject has a confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements
- The subject is lost to follow-up
- Completed 24 months of uninterrupted treatment with pembrolizumab. Administrative reasons

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

Note: The treatment plan is for approximately 12 pembrolizumab infusions (36 weeks) treatment.

5.9.1 Discontinuation of Study Therapy after CR

Discontinuation of treatment may be considered for subjects who have attained a confirmed CR that have been treated for at least 24 weeks with pembrolizumab and had at least two treatments with pembrolizumab beyond the date when the initial CR was declaredThere is no retreatment phase on this protocol.

Subject Replacement Strategy

Subjects with an apparent CR after B1, 9 weeks of pembrolizumab, may be treated with up to 12 doses pembrolizumab, but no IL-2, at the investigator discretion. These will be replaced (up to the total enrollment target of 26).

Subjects with clinical events after initial B1 dose of pembrolizumab, but then later not meeting usual criteria for treatment with IL-2 at the point in time of the B2W2 IL-2 start, despite having previously met them before start – for example new onset rapid atrial fibrillation – may continue on pembrolizumab at treating physician discretion, up to 12 doses. These will be replaced (up to the total enrollment target of 26).

5.10 Clinical Criteria for Early Trial Termination

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

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

2. Poor adherence to protocol and regulatory requirements

3. Incidence or severity of adverse drug reaction in this or other studies indicates a potential health hazard to subjects

4. Plans to modify or discontinue the development of the study drug

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

6.0 TRIAL FLOW CHART *FIGURE 6: STUDY FLOW CHART*

6.1

Trial Period:	Screening Phase		Treatment Cycles: Monotherapy (B1, B4, cE)				Treatment Cycles: IL2 combination (B2, B3)				End of Treatment	Post-Treatment		
Treatment Cycle/Title:	Pre-screening (Visit 1)	Main Study Screening (Visit 2)	w1	w4	w7	**eval** w9	w1	w4	W7	Eval w9	Discontin-uation	Safety Follow-up	Follow Up Visits	Survival Follow-Up
IL2 weekly: W2 or W5 = 2-9 days after pembro. W3 or W6 = 6-9 days after W2 or W5			B1 <d1> *			± 5	W2 W3	W5 W6		± 5	At time of Discon-uation	30 days post discon-uation visit.	Every 2 months post discon-uation.	Every 3 months (by phone okay)
Pembrolizumab Scheduling Window (Days):		-28 to 0	B4 ± 3	± 3	± 3		± 3	± 3	± 3		± 10	± 10	± 10	± 30
Administrative Procedures														
Pre-screening	x													
Informed Consent		x												
Inclusion/Exclusion Criteria		x												
Demographics and Medical History	x													
Prior and Concomitant Medication Review		x												
Pembrol Treatment Administration			x	x	x		x	x	x					
IL-2 treatment called “W2” or “W5”							x	x						
IL-2 treatment called “W3” or “W6”							x	x						
Post-study anticancer therapy status											x			
Survival Status											x	x	x	x

Trial Period:	**Screening Phase**		**Treatment Cycles**								**End of Treatment**	**Post-Treatment**		
			Monotherapy (B1, B4, cE)				**IL2 combination (B2, B3)**							
Treatment Cycle/Title:	Pre-screening (Visit 1)	Main Study Screening (Visit 2)	w1	w4	w7	**eval** w9	w1	w4	W7	Eval w9	Discontin-uation	Safety Follow-up	Follow Up Visits	Survival Follow-Up
IL2 weekly: W2 or W5 = 2-9 days after pembro. W3 or W6 = 6-9 days after W2 or W5			B1 <d1> *			± 5	W2 W3	W5 W6		± 5	At time of Discon-uation	30 days post discon-uation visit.	Every 2 months post discon-uation.	Every 3 months (by phone okay)
Pembrolizumab Scheduling Window (Days):		-28 to 0	B4 ± 3	± 3	± 3		± 3	± 3	± 3		± 10	± 10	± 10	± 30
Clinical Procedures/Assessments														
Review Adverse Events			x	x	x		x	x	x		x			
Full Physical Examination		x				x	W2 W3	W5 W6		x	x	x		none
Directed Physical Examination	x		x	x	x		W1	W4	x				x	
Vital Signs and Weight		x	x	x	x	x	x	x	x		x			
ECOG Performance Status	x	x	x				x				x	x	x	x
Laboratory Procedures/Assessments: analysis performed by LOCAL laboratory														
Pregnancy Test – Urine or Serum β-HCG (only for women of child bearing potential; must be <72 hours before first dose.)			x	x	x		x	x	x		x			
PT/INR and aPTT		x												
CBC with Differential & Comprehensive Serum Chemistry Panel		x					W1 W2	W4 W5	x			x	x	

Trial Period:	**Screening Phase**		**Treatment Cycles**								**End of Treatment**	**Post-Treatment**		
			Monotherapy (B1, B4, cE)				**IL2 combination (B2, B3)**							
Treatment Cycle/Title:	Pre-screening (Visit 1)	Main Study Screening (Visit 2)	w1	w4	w7	**eval** w9	w1	w4	W7	Eval w9	Discontin-uation	Safety Follow-up	Follow Up Visits	Survival Follow-Up
IL2 weekly: W2 or W5 = 2-9 days after pembro. W3 or W6 = 6-9 days after W2 or W5			B1 <d1> *			± 5	W2 W3	W5 W6		± 5	At time of Discon-uation	30 days post discon-uation visit.	Every 2 months post discon-uation.	Every 3 months (by phone okay)
Pembrolizumab Scheduling Window (Days):		-28 to 0	B4 ± 3	± 3	± 3		± 3	± 3	± 3		± 10	± 10	± 10	± 30
							W3	W6						
Urinalysis		x	x				W2 W3	W5 W6			x	x	x	
T3, FreeT4 and TSH			x				x				x		x	
Efficacy Measurements														
Tumor Imaging		x				x				x			x	
Tumor Biopsies/Archival Tissue Collection/Correlative Studies Blood														
Archival or Newly Obtained TissueCollection **		x												
Correlative Studies Blood Collection** (30 ml per time point)		Pre-treatment (or B1W1)	B4 W1				Pre B2 W2	At B2 W4						
* B1W1 = this is by definition the first treatment day, so +/- 3 does not apply. B4: the +/-3 does apply.														

** Correlative blood specimen collection procedure:

Vaccutainer type or CPT tubes will be used for collection of 30 ml peripheral blood specimens. The tubes should be filled and inverted 8-10 times after collection and prior to separation. The samples should be processed within 8 hours of collection and should not be refrigerated or frozen.

Peripheral blood mononuclear cells (PBMC) will be isolated by density centrifugation using Ficoll™ and the cells will be frozen in 10% DMSO, 90% fetal calf serum and stored in vapor phase liquid nitrogen until ready for testing.

Serum will be isolated by centrifugation and frozen similarly.

Specimens will be stored in the Tissue Core repository.

The PI will designate which specimens will be analyzed, based on factors including disease response and dose delivery.

6.2 Additional retreatment will not be part of this protocol

7.1 TRIAL PROCEDURES

7.2 Trial Procedures

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

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

7.2.1 Administrative Procedures

7.2.1.1 Informed Consent

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

General Informed Consent

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

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

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

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

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

7.2.1.2 Inclusion/Exclusion Criteria

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

7.2.1.3 Medical History

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

7.2.1.4 Prior and Concomitant Medications Review

7.1.1.4.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the subject within 28 days before starting the trial. Treatment for the disease for which the subject has enrolled in this study will be recorded separately and not listed as a prior medication.

7.1.1.4.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the subject during the trial. All medications related to reportable SAEs and ECIs should be recorded as defined in Section 7.2.

7.1.1.5 Disease Details and Treatments

7.1.1.5.1 Disease Details

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

7.1.1.5.2 Prior Treatment Details

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

7.1.1.5.3 Subsequent Anti-Cancer Therapy Status

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

7.1.1.6 Assignment of Screening Number

This will be through the Oncore computer program.

7.1.1.7 Assignment of Rando.mization Number

Not applicable to this protocol

7.1.1.8 Trial Compliance (Medication/Diet/Activity/Other)

Medication compliance documentation: same as infusion schedule.

Concomitant medication compliance: At least once per treatment block (9 weeks).

Activity compliance: No restrictions; no data collected.

Diet compliance: No restrictions; no data collected.

Other compliance: At review of other treatments.

7.1.2 Clinical Procedures/Assessments

7.1.2.1 Adverse Event (AE) Monitoring

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

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

Note: Events that are consistent with the expected adverse events of IL-2 therapy, as annotated on the Proleukin ™ prescribing information, and which resolve along the expected time course (generally within a few days) are to be distinguished from pembrolizumab irAEs.

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

7.1.2.2 Full Physical Exam

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

7.1.2.3 Directed Physical Exam

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

7.1.2.4 Vital Signs

The investigator or qualified designee will take vital signs at screening, prior to the administration of each dose of trial treatment and at treatment discontinuation as specified in the Trial Flow Chart (Section 6.0). Vital signs should include temperature, pulse, respiratory rate, weight and blood pressure. Height need be measured at screening only.

7.1.2.5 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG status (see Section 11.1) at screening, prior to the administration of each dose of trial treatment and discontinuation of trial treatment as specified in the Trial Flow Chart.

7.1.2.6 Tumor Imaging and Assessment of Disease

About every 9-12 weeks, during the treatment cycles, and about every 2-3 months , through 1 year, then as clinically indicated after that, using CT or MRI, at the discretion of the treating physician. Generally, the same modality will be used throughout, and should cover all known sites of disease.

Several days interval should be used between administration of IV contrast and administration of high dose IL-2. The protocol schedule typically puts these at least a week apart.

7.2 Tumor Tissue Collection and Correlative Studies Blood Sampling

The following tissue and blood markers will be considered for correlative testing.

(1) Quantitation of circulating cells with flow cytometry counts for cells with lymphocyte phenotypes of CD3+, CD4+, T-regulatory, CD8+, NK+, MDSC, or DC, and conventional differential for granulocytes, platelets or other subtypes.

(2) On the pretreatment tumor specimen, quantitation of infiltrating leukocytes that are positive for CD3, CD4 or CD8, by immunohistochemistry.

(3) On the pretreatment tumor specimen, quantiation of PD-L1.

(4) Quantitation of serum cytokines and other proteins, including but not limited to: CXCL9, CXCL10

(5) CD8+ lymphocyte analyses of gene expression; using the NanoString product, Multiplexed Cancer Immune Response Analysis nCounter® PanCancer Immune Profiling Panel for Gene Expression. A similar assay on other leukocyte subsets may be performed.

The analysis plan for these secondary correlative endpoints is given in Section 8.5.

7.2.1 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below: Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

Laboratory tests for hematology, chemistry, urinalysis, and others are specified in Table 5.

Table 5 Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Blood	Serum β-human chorionic gonadotropin†
Hemoglobin	Alkaline phosphatase	Glucose	(β-hCG)†
Platelet count	Alanine aminotransferase (ALT)	Protein	PT (INR)
WBC (total and differential)	Aspartate aminotransferase (AST)	Specific gravity	aPTT
Red Blood Cell Count	Lactate dehydrogenase (LDH)	Microscopic exam *(If abnormal)*	Total thriiodothyronine (T3)
Absolute Neutrophil Count	Carbon Dioxide ‡	results are noted	Free thyroxine (T4)
Absolute Lymphocyte Count	*(CO_2 or biocarbonate)*	Urine pregnancy test †	Thyroid stimulating hormone (TSH)
	Uric Acid		PK [not on this protocol]
	Calcium		
	Chloride		Blood for correlative studies
	Glucose		
	Phosphorus		
	Potassium		
	Sodium		
	Magnesium		
	Total Bilirubin		
	Direct Bilirubin *(If total bilirubin is elevated above the upper limit of normal)*		
	Total protein		
	Blood Urea Nitrogen		

† Perform on women of childbearing potential only. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required.

‡ If considered standard of care in your region.

Laboratory tests timing and evaluation are described in section 6.1 .

7.2.1.1 Pharmacokinetic/Pharmacodynamic Evaluations

7.2.1.1.1 Blood Collection for Serum Pembrolizumab

There is no pembrolizumab pharmacokinetics evaluation.

7.2.1.1.2 Blood Collection for Anti-Pembrolizumab Antibodies

The serum from the B1W1 and B4W1 will be used for this assay.

Missing data will not be considered a deviation for this assay.

Specimens will be under standard Tissue Core program procedures for collection and storage.

7.2.2 Other Procedures

7.2.2.1 Withdrawal/Discontinuation

When a subject discontinues/withdraws prior to trial completion, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.2 - Assessing and Recording Adverse Events. Subjects who a) attain a CR or b) complete all of the on-protocol treatment with pembrolizumab may discontinue treatment. After discontinuing treatment following assessment of CR, these subjects should return to the site for a Safety Follow-up Visit and then the Follow-Up Period of the study.

7.2.3 Visit Requirements

Visit requirements are outlined in Section 6.0 - Trial Flow Chart. Specific procedure-related details are provided above in Section 7.1 - Trial Procedures.

7.2.3.1 Screening period

Evaluation of eligibility for inclusion and absence of exclusion. Target less than 30 days from consent to start of treatment. Tests as specified in the inclusion and exclusion criteria should be scheduled and evaluated.

7.2.3.2 Treatment Period

Approximately 36 weeks overall, divided into 4 blocks of 9 weeks each.

7.2.3.3 Post-Treatment Visits

Every 2-3 months after the end of the treatment, through 24 months. These are necessary to accommodate screening for the occurrence of late adverse events.

Safety Follow-Up Visit

The mandatory Safety Follow-Up Visit should be conducted approximately 30 days after the last dose of trial treatment or before the initiation of a new anti-cancer treatment, whichever comes first. All AEs that occur prior to the Safety Follow-Up Visit should be recorded. Subjects with an AE of Grade > 1 will be followed until the resolution of the AE to Grade 0-1 or until the beginning of a new anti-neoplastic therapy, whichever occurs first. SAEs that occur within 90 days of the end of treatment or before initiation of a new anti-cancer treatment should also be followed and recorded. Subjects who are eligible for retreatment with pembrolizumab (as described in Section 7.1.5.5) may have up to two safety follow-up visits, one after the Treatment Period and one after the Second Course Phase.

Follow-up Visits

Subjects who discontinue trial treatment for a reason other than disease progression will move into the Follow-Up Phase and should be assessed as clinically indicated by radiologic imaging to monitor disease status, usually about every 2-3 months during the first year. After 1 year, usually every 3 months. Every effort should be made to collect information regarding disease status until the start of new anti-neoplastic therapy, disease progression, death, end of the study. Information regarding post-study anti-neoplastic treatment will be collected if new treatment is initiated.

Survival Follow-up

Once a subject experiences confirmed disease progression or starts a new anti-cancer therapy, the subject moves into the survival follow-up phase and should be contacted by telephone or other conventional communication method every 3 months to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

Second Course Phase (Retreatment Period)

There is no retreatment course within this protocol.

7.3 Assessing and Recording Adverse Events

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

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

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

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

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

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

All adverse events will be recorded from the time of Cycle 1 Day 1 through 30 days following cessation of treatment and at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in section 7.2.3.1. For purposes of this trial only lab findings that are deemed clinically significant and related to Pembrolizumab by the Investigator will be recorded. Only Adverse events or ESI's related to Pembrolizumb will be recorded. Any Expected Adverse Event related to the administration of IL-2 will not be recorded in the CRF's.

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

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

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

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

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

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

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

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

7.3.3 Immediate Reporting of Adverse Events to Merck and to Prometheus

7.3.3.1 Merck Serious Adverse Events

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

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

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

Any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study that occurs to any subject from

the time the consent is signed through 90 days following cessation of treatment, or the initiation of new anti-cancer therapy, whichever is earlier, whether or not related to Merck product, must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety.

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

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

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

7ADDITIONALLY:

Reporting to Prometheus

A copy of any SAE report submitted to the IRB must be sent to Prometheus Laboratories.

If Proleukin® (Aldesleukin, IL-2) is a suspect or co-suspect drug reported on the FDA Form 3500A MedWatch report, Prometheus Laboratories also requests a courtesy copy of the FDA Form 3500A MedWatch report that was submitted to the US Food and Drug Administration, via email or fax, to Drug Safety and Pharmacovigilance at Prometheus Laboratories, Inc.

The report should include the site contact information.

Drug Safety Email: drugsafety@prometheuslabs.com

Drug Safety Fax: (858) 754-3046

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

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

7.3.3.2 Events of Clinical Interest

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

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

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

*Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The trial site guidance for assessment and follow up of these criteria can be found in the Investigator Trial File Binder (or equivalent).

3. Additional adverse events:

A separate guidance document has been provided entitled “Event of Clinical Interest Guidance Document” (previously entitled, “Event of Clinical Interest and Immune-Related Adverse Event Guidance Document”). This document provides guidance regarding identification, evaluation and management of ECIs and irAEs.

ECIs (both non-serious and serious adverse events) identified in this guidance document from the date of first dose through 90 days following cessation of treatment, or 30 days after the initiation of a new anticancer therapy, whichever is earlier, need to be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220), regardless of attribution to study treatment, consistent with standard SAE reporting guidelines.

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

7.3.4 Evaluating Adverse Events

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

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

For the purpose of this study, IL-2 AEs/SAEs will be recorded and reported as follows:

Table 6a: AE evaluation timline

Record and Report:	Begin	End
AEs leading to permanent dosing discontinuation of either pembrolizumab or HD IL-2 AEs ≥ Severity Grade 3 occurring after the HD IL-2 administration dates Unexpected (according to medical judgment) AEs	Following first dose of IL-2	Patient has terminated, withdrawn, or completed the study

Pre-existing conditions (i.e., noted before study drug administration) should not be reported as AEs unless they worsen (i.e., become more severe or more frequent) following administration of either study drug.

Metastatic clear-cell Renal Cell Carcinoma disease progression is study endpoint information and should not be reported as an adverse event.

Events **not** considered to be serious adverse events are hospitalizations for:

- routine treatment or monitoring of the studied indication, not associated with any deterioration in condition, or for elective procedures;
- elective or pre-planned treatment for a pre-existing condition that did not worsen;
- emergency outpatient treatment for an event not fulfilling the serious criteria; outlined above and not resulting in inpatient admission;

- and respite care.

Table 6b Evaluating Adverse Events with respect to pembrolizumab

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

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

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

7.3.5 Sponsor Responsibility for Reporting Adverse Events

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

8.1 STATISTICAL ANALYSIS PLAN

8.2 Statistical Analysis Plan Summary

Overall response rate (ORR) and the 95% confidence interval of that estimate will be obtained through binomial distribution theory, using the ITT population, with a one-sided endpoint, for the primary endpoint. Progression free survival, overall survival, landmark one-year progression free survival, landmark one-year overall survival will be obtained by Kaplan-Meier method.

The adverse events will be tabulated descriptively, by grade. All AEs will be summarized by system organ class and preferred term. Listings and summary tables will be provided. Separate data listings and summaries will be presented for all serious adverse events (SAEs) and deaths.

The correlative study tests will be analyzed as an exploratory assessment, or as part of a separate correlative protocol.

8.3 Statistical Analysis

Study population definitions

The primary endpoint, ORR, will be estimated, along with a with one-sided 95% confidence interval, counting evaluable patients (the "combination treatment population") getting at least one per-protocol dose of IL-2, using binomial distribution theory.

The response assessment and safety assessment populations are defined for the analyses as follows:

FIGURE 7: Population definitions

name	*description*
Intent to treat (ITT) population (ITT efficacy analysis)	Eligible and registered
Ever-treated population (Safety evaluation population)	At least one dose of pembrolizumab
Combination treatment population	At least one dose of pembrolizumab (start of block B1) and at least one dose of IL-2

	(usually indicating a start of block B2, and usually at least 4 doses of pembrolizumab).
Combination threshold population	At least 6 doses of pembrolizumab and at least 10 doses of IL-2 (In any block).

8.4 Planned primary reporting analyses

Analysis: Overall response rate ORR is defined with confirmation of the response status CR or PR among the combination treatment population patients; the binomial estimate and its one-sided 95% confidence interval will be reported.

Analysis: Overall survival (OS) of ITT patients counting from the eligible date to death from any cause, or censored on end of known follow up, either within this study or in the PROCLAIM registry.

Analysis: Progression-free survival (PFS) of ITT patients from the confirmed eligible date to the first occurrence of disease progression or death, from any cause, or lost to follow up, whichever is earliest; or censored at last follow-up during study.

Kaplan-Meier method will be used for OS as well as PFS analysis.

The Simon minimax two-stage design (Simon, 1989) with a 10% type I error and 90% power will be used to test the null hypothesis that overall response rate (CR+PR) ≤ 0.20 versus the alternative hypothesis of overall response rate >0.45. In the 1st stage, 15 patients will be treated. If 3 or fewer respond, the trial will be terminated. If 4 or more respond, an additional 9 evaluable patients (the "combination treatment population") will be studied in the 2nd stage (a total of n=24 evaluable patients). If the total number responding is less than or equal to 7, the drug is rejected. This design has an expected sample size of 18 patients with a probability of early termination of 0.65.

The overall total number of patients, counting patients with at least one dose of IL-2 administered, will be up to n =26. This will accommodate replacement of subjects who are in the intent-to-treat(ITT) population, but not part of the main developmental objective of the study, which is the combination treatment population.

Secondary analysis of other populations that are defined above.

These include "ever treated", "combination treatment" and "combination threshold treatment" as described above.

8.5 Adverse Event tabulation and classification

FIGURE 8: AE classification by population

AEs will be classified in each of these categories:

Population name / *AE category*	ITT population	Ever-treated population	Combination ever-treated population	Combination Threshold population
	After enrollment but before any study drug administration	After administration of at least one dose of pembrolizumab	Among those with at least one dose of pembrolizumab and at least one dose of IL-2	Among those with at least 6 doses of pembrolizumab and at least 10 doses of IL-2
Unrelated				
Possibly related				
Probably related				
Definitely related				

AEs *possibly, probably or definitely* related to the study treatment (shaded area) will be summarized by system organ class and preferred term.

Listings and summary tables will be provided.

Separate data listings and summaries will be presented for all serious adverse events (SAEs) and deaths.

1. Safety monitoring: Sequential boundaries will be used to monitor dose-limiting toxicity rate. The method is developed by Ivanova, Qaqish, and Schell (Biometrics, 2005) Briefly, the accrual of new patients to the trial will be suspended to accommodate re-evaluation of safety issues if the number of patients with dose-limiting toxicities is equal to or exceeds b_n out of n patients who are part of the *combination treatment population* (see table). This is a Pocock-type stopping boundary that yields the probability of crossing the boundary at most 0.05 when the rate of dose-limiting toxicity is equal to the acceptable rate 0.15.

Patients who have already enrolled, but not yet started on treatment with any pembrolizumab, at a point in time at which the accrual was suspended may be treated at the discretion of the investigator based on the safety evaluation.

FIGURE 9: Table of Pocock boundary evaluation

Table for number of patients k and Pocock boundary $b_{k.}$																										
Number of Patients, k	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24		
Boundary, b_n	-	-	3	3	4	4	4	5	5	5	5	6	6	6	6	7	7	7	7	8	8	8	8	8		

If the number of patients k who have DLT events that are *possibly, probably or definitely* related equals or exceeds the boundary b_k, the accrual to the trial will be suspended pending reevaluating toxicity by study PI and the Protocol Monitor Committee (PMC). This may include recommendations on patients who have already started on treatment.

The DLT events for this safety purpose will *exclude* events that are judged by the PI to be typical for IL-2 treatment, referencing the experience as described in the package insert for Proleukin™ *and* have resolved by the point in time that the next dose of pembrolizumab is due. The DLT events to be counted here will include at least those defined as in section 7.3.4 as these:

- AEs leading to permanent dosing discontinuation of either pembrolizumab or HD IL-2
- AEs ≥ Severity Grade 3 occurring after the HD IL-2 administration dates
- Unexpected (according to medical judgment) AEs
- Additionally, other events that the PI may designate.

8.6 Correlative studies on specimens of tumor and of blood specimens:

These are all secondary endpoints,

Responders versus remaining patients will be compared.

The following tissue markers will be considered for correlative testing.

(1) Quantitation of circulating cells with flow cytometry counts for cells with lymphocyte phenotypes of CD3+, CD4+, T-regulatory, CD8+, NK+, MDSC, or DC, and conventional

differential for granulocytes, platelets or other subtypes. The relevant ratios, such as DC: MDSC ratio; CD4+ : CD4/FoxP3+ ratio; CD8+ : NK cell ratio will be computed.

(2) On the pretreatment tumor specimen, quantitation of infiltrating leukocytes that are positive for CD3, CD4 or CD8, by immunohistochemistry.

(3) On the pretreatment tumor specimen, quantiation of PD-L1.

(4) Quantitation of serum cytokines including but not limited to: CXCL9, CXCL10

If the data follow a normal distribution, t test will be used for biomarker level comparison. If the data do not follow normal distribution then a power transformation (e.g. square-root, log) or non-parametric Wilcoxon rank-sum test approach will be adopted. The Bonferroni-Holm approach will be used to account for multiple testing to control type I error at 5%. Some tests may be dropped from the multiple testing group prior to analysis after the overall distribution of the biomarker is examined, but before it is divided by response group. Tests outside the multiple testing group will be studied at alpha = .05 individually, and considered as exploratory analyses.

(5) CD8+ lymphocyte subset analyses of gene expression; using the NanoString product, Multiplexed Cancer Immune Response Analysis nCounter® PanCancer Immune Profiling Panel for Gene Expression. A similar assay on other leukocyte subsets may be performed.

The 760 genes expressed will be compared for the responders versus the nonresponders, for the baseline specimens.

The 760 genes expressed will be compared for the specimens after the 3 on treatment specimens versus baseline specimens.

These analyses will identify genes for which there is a statistically significant difference of expression level. The description of these genes' expression difference will be the endpoint, to address the hypothesis that differences of CD8+ gene expression are a consequence of the treatment with these medications that have targets on lymphocytes.

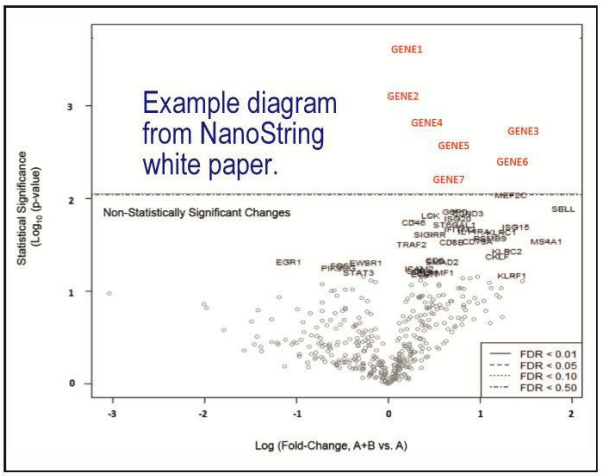

Figure 10 NanoString technology differentiates gene expression changes in response to distinct immunotherapies.

The validation of the included genes are relevant to immune assessment is not a point of discussion to be repeated in the text of this protocol. The reader must refer to the white paper. These are the links:

http://nanostring.yipkos.com/service/documents/ASCO2016/White%20Papers/NanoString_IO_White paper_Final%20(005).pdf

http://nanostring.yipkos.com/service/documents/ASCO2016/White%20Papers/LBL-10117-02_WP_PanCancer_Immune_Profiling.pdf

9.1 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

9.2 Investigational Product

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

Clinical Supplies will be provided by Merck as summarized in Table 7.

Table 7 Product Descriptions

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

9.3 Packaging and Labeling Information

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

9.4 Clinical Supplies Disclosure

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

9.5 Storage and Handling Requirements

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label.

Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site.

Clinical supplies may not be used for any purpose other than that stated in the protocol.

9.6 Returns and Reconciliation

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

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

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10.1 ADMINISTRATIVE AND REGULATORY DETAILS

10.2 Confidentiality

The data will be maintained on the ONCORE program at the Moffitt Cancer Center. No personally identifiable data will be published.

Outcome data will be available to Merck and to Prometheus.

10.3 Compliance with Financial Disclosure Requirements

All Financial disclosures, relationship to sponsors, will be organized as required by law.

10.4 Compliance with Law, Audit and Debarment

All applicable laws will be complied.

No debarred physicians will be study investigators.

10.5 Compliance with Trial Registration and Results Posting Requirements

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

10.6 Quality Management System and the PMC

The principal investigator has the authority to stop the study, including stopping accrual, or stopping protocol-treatment.

The principal Investigator is ultimately responsible for the study.

The principal Investigator will review the Serious Adverse Events

The principal investigator has the authority to stop the study, including stopping accrual, or stopping protocol-treatment.

The adverse event data will be reviewed by the principal investigator in conjunction with the study biostatisticians.
This is an investigator initiated trial, that will be monitored according to the Moffitt Cancer Center Policy for Monitoring of Investigator Initiated Clinical Research. Data will be captured in the Oncore computer database program.

Regulatory documents and case report forms will be monitored internally, according to Moffitt Cancer Center Monitoring Policies.

Monitoring will be performed regularly to verify data are accurate, complete and verifiable from source documents.

Monitoring will be performed to ensure that the conduct of the trial is in compliance with currently approved protocol, and with Good Clinical Practice *guidelines*, and with applicable regulatory requirements.

The study will be reviewed by the PMC for data and safety monitoring. *This is the standard Moffitt Cancer Center Data Safety Monitoring Plan for investigator initiated studies.* The PMC monitors for adverse event reporting, for data and safety monitoring, and internal audit findings. The PMC, upon review of an agenda item, may approve the study for continuation, recommend revisions, or suspend or close a protocol.

10.7 Data Management

Data will be tabulated from source documents and placed into custom forms on the ONCORE program at Moffitt Cancer Center.

11.1 APPENDICES

11.2 ECOG Performance Status

FIGURE 10: ECOG PS table

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

* As published in Am. J. Clin. Oncol.: *Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.* The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.

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

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

11.4 NOTE: Response Evaluation are in section 5.3

11.5 NOTE: Events of Clinical Interest Guidance Document is a separate document

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