COVER PAGE

Title of Protocol	
A Phase I Trial of Interleukin-2 (Aldesleukin) and Pembrolizumab Combination Therapy for Patients with Advanced Renal Cell Carcinoma	
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List of Abbreviations	
5HT3	5-hydroxytryptamine3 receptor
ADL	Activities of daily living
AE	Adverse Event
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
attn	attention
B cell	Bursa (or bone marrow)-derived lymphocyte
BCG	Bacillus Calmette–Guérin
β-HCG	Beta-Human chorionic gonadotropin
BMP	Basic metabolic panel
BP	Blood pressure
CBC	Complete blood count
cc	cubic centimeter
CD	Cluster of differentiation
CDR	Complementarity determining region
CNA	Copy number alteration
CNS	Central nervous system
CPK	Creatine phosphokinase
CR	Complete response
CRC	Colorectal cancer
CrCl	Creatinine Clearance
CRF	Case report form
CRS	(Cancer Consortium) Clinical Research Support
CSA	Controlled Substance Act (Title II)
CT	Computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	Cytotoxic T-lymphocyte-associated Antigen-4
D5LR	5% Dextrose in Lactated Ringer`s solution
DCR	Disease control rate
diff	White blood cell differential
DKA	Diabetic ketoacidosis
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid

DSMC	Data Safety Monitoring Committee
DSMP	Data and Safety Monitoring Plan
EC	Ethics committee
ECG/EKG	Electrocardiogram
ECI	Event of clinical interest
ECOG	Eastern Cooperative Oncology Group
EOT	End of treatment
ERC	Ethics Review Committee
EU	European Union
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FDAMA	Food and Drug Administration Modernization Act
FEV1	Forced expiratory volume in 1 second
FFPE	Formalin fixed, paraffin embedded
Fred Hutch	Fred Hutchinson Cancer Center
FT4	Free T4
FVC	Forced vital capacity
GI	Gastrointestinal specialist (Gastroenterology)
GFR	Glomerular filtration rate
Hct	Hematocrit
HCV	Hepatitis C virus
HD	High-Dose
HDIL-2	High-Dose Interleukin-2
HIF	Hypoxia-inducible factor
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
hr	hour
HR	Hazard ratio
HSV	Herpes simplex virus
IB	Investigator's brochure
ICU	Intensive care unit
IEC	Independent ethics committee
IFN-α	interferon-alfa
IFN-γ	Interferon-gamma
Ig	Immunoglobulin
IHC	Immunohistochemistry
IL-2	Interleukin-2

IND	Investigational New Drug
INR	International normalized ratio
irAEs	immune-related Adverse Events
IRB	Institutional Review Board
IV	Intravenous
K	potassium
kg	kilogram
L	Liter
LD/LDH	Lactate dehydrogenase
LFT	Liver function tests
LVEF	Left ventricular ejection fraction
MAP	Mean arterial pressure
mAb	monoclonal antibody
mcg	microgram
mcL	microliter
MCV	Mean corpuscular volume
MD	Medical doctor
mg	milligram
Mg	Magnesium
min	minute
mL	milliliter
mmol	millimole
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
mTOR	mammalian Target of Rapamycin
MUGA	Multiple-Gated Acquisition Scan
N	Number
NCI	National Cancer Institute
NK	Natural killer cell
NSAID	Nonsteroidal anti-inflammatory drug
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OTC	Over-the-counter
PATS	Protocol Accrual Tracking System
PD	Progressive disease
PD1	Programmed Cell Death 1
PD-L1	Programmed Cell Death 1 - Ligand 1

PD-L2	Programmed Cell Death 1 - Ligand 2
PFS	Progression-free survival
pH	potential of Hydrogen
PhD	Doctor of Philosophy
Phos	Phosphate
PICC	Peripherally inserted central catheter
PK	Pharmacokinetic
Plts	Platelets
PMDA	Pharmaceutical and Medical Devices Agency
PO	Per os (by mouth)
PR	Partial response
PT	Protime
Q1h	Every hour
Q2W	Every 2 weeks
Q3W	Every 3 weeks
Q4h	Every 4 hours
RCC	Renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RN	Registered nurse
R/O	Rule out
RR	Risk ratio
SAE	Serious adverse event
SCCA	Seattle Cancer Care Alliance
SD	Stable disease
SDRB	Safety Data Review Board
SQ	Subcutaneous
SVT	Supraventricular tachycardia
T1DM	Type 1 diabetes mellitus
T cell	Thymus-derived lymphocyte
TCR	T cell receptor
TIL	Tumor-infiltrating lymphocyte
Teff	Effector T Cell
Treg	Regulatory T cell
TSH	Thyroid-stimulating hormone
U	Unit
ULN	Upper limit of normal
URI	Upper respiratory infection

UTI	Urinary tract infection
UW	University of Washington
VEGF	Vascular endothelial growth factor
VHL	Von Hippel-Lindau
VT	Ventricular tachycardia
WBC	White blood cell
wk	week

1.0 TRIAL SUMMARY

Abbreviated Title	IL-2 and Pembrolizumab for Advanced RCC
Trial Phase	Phase I
IND Number	133532
Clinical Indication	Advanced or metastatic clear cell RCC
Trial Type	Therapeutic
Type of control	Historical control
Route of administration	SQ IL-2; IV IL-2 IV pembrolizumab
Trial Blinding	None
Treatment Groups	Dose Level 1: SQ IL-2 plus IV pembrolizumab; Dose Levels 2 and 3: IV IL-2 plus IV pembrolizumab
Number of trial subjects	N=12 to 15
Estimated Enrollment Period	36 months
Estimated duration of trial	5 years
Duration of Participation	Maximum of 3 cycles of treatment (36 weeks) with follow-up.

2.0 TRIAL DESIGN

2.1 Trial Design

This is a phase I, open-label, dose escalation and conditional cohort expansion at the maximum tolerated dose (MTD) of Interleukin-2 (IL-2; aldesleukin), a soluble cytokine growth factor for T lymphocytes, in combination with pembrolizumab (MK-3475), a humanized monoclonal antibody (mAb) of the IgG4/kappa isotype designed to target the Programmed Death 1 (PD1) membrane receptor on activated T lymphocytes. Treatment is for patients with advanced or metastatic clear cell renal cell carcinoma (RCC).

The study will consist of 3 periods: Screening (up to 28 days), Treatment (up to three 12-week courses), and Follow-Up (up to 1 year). Each treatment course ("course" nomenclature is by the conventions of IL-2 treatment) is comprised of 4 doses (cycles) of pembrolizumab given by iv infusion every 3 weeks combined with 1 cycle of IL-2 given by SQ administration daily 5 days/week for 6 weeks at Dose Level 1; or by IV bolus infusion (Dose Level 2 and 3) every 8 hours to a maximum of 14 doses on weeks 1 (cycle 1) and 4 (cycle 2) of a treatment course. Investigator tumor response assessment (by RECIST v1.1) must be completed before the first dose of the next treatment course. The maximum number of on-study treatment courses will be three.

Following completion of treatment, patients with ongoing disease control (CR, PR, or SD) will enter Surveillance Follow-Up. Disease status will be reassessed every 3 months for up to 1-year duration. Patients with disease control completing one year of Surveillance Follow-Up or patients with disease progression will enter Survival Follow-Up to study completion.

2.2 Dose Escalation

The study will use a 3 + 3 trial design for IL-2 dose escalation. Rules for dose escalations are described in Section 5.2.1.2. Definitions for dose-limiting toxicities (DLT's) are described in Section 5.2.1.3.

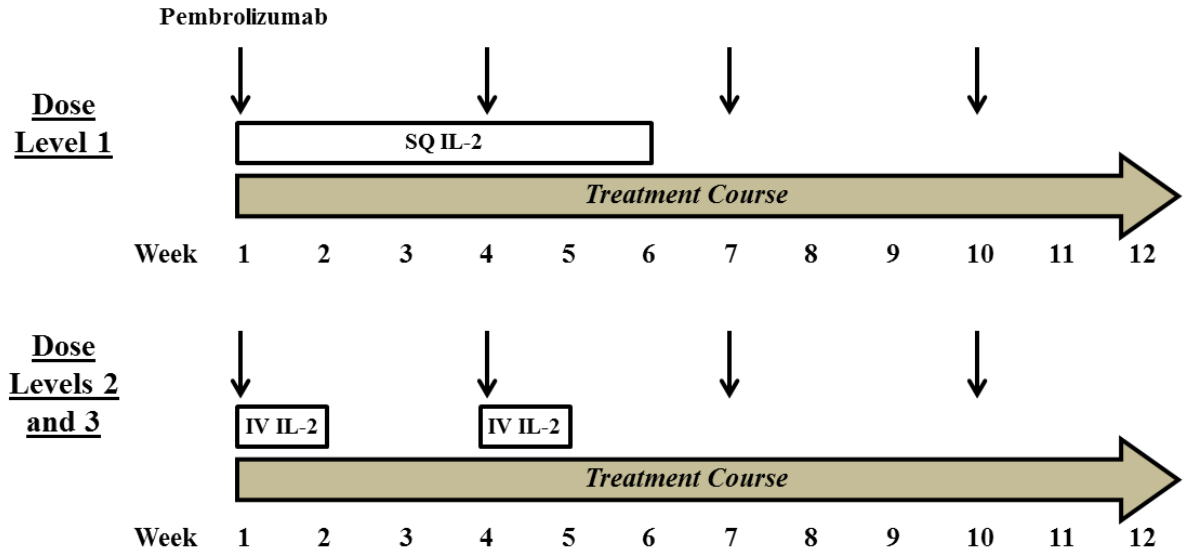
2.3 Cohort Expansion

On completion of Dose Escalation including data and safety analysis, the Principal Investigator and Merck will assess the feasibility to enroll additional patients at Dose Level 3 (or at the MTD Dose Level) to gain further preliminary insight into anti-tumor efficacy. Commitment to open the Expansion Cohort and modification of the target enrollment will require protocol amendment.

Table 1 Drug Dose and Schedule

Cohort	Pembrolizumab	IL-2	
1	200 mg Q3W	250,000 U/kg/dose 5 days/wk; wk 1; 125,000 U/kg/dose 5 days/wk; wks 2-6	*SQ Dose Level 1*
2	200 mg Q3W	72,000 U/kg iv q 8 hrs x 14 doses; d2-6 and 23-27 of a 12 week course	*IV Bolus Dose Level 2*
3	200 mg Q3W	600,000 U/kg iv q 8 hrs x 14 doses; d2-6 and 23-27 of a 12 week course	*IV Bolus Dose Level 3*

Figure 1 Trial Diagram



3.0 OBJECTIVES

The purpose of this study is to characterize the safety, tolerability, preliminary anti-tumor activity, and immunoregulatory (pharmacodynamic) activity of pembrolizumab in combination with IL-2 in patients with metastatic clear cell RCC. The goal of this study is to demonstrate adequate safety and tolerability of the combination of pembrolizumab and IL-2 so as to permit further testing. Information gathered will inform the dose and schedule of administration of pembrolizumab with IL-2 in future studies.

3.1 Primary Objective

- To evaluate the safety and tolerability of IL-2 combined with pembrolizumab in patients with metastatic clear cell RCC.

3.2 Secondary Objective

- To assess preliminary antitumor activity of pembrolizumab in combination with IL-2.

3.3 Exploratory Objectives

- To investigate the association of PD-L1 protein expression by pretreatment tumor with response to treatment.
- To investigate the association of regulatory T cell (Treg) frequency and Treg to effector T cell (Teff) ratios in peripheral blood and tumor tissue with response to therapy.
- To investigate the association of *de novo* serological and cellular responses against the ubiquitous RCC tumor antigen 5T4 with response to therapy.
- To investigate the association of tumor infiltrating lymphocyte (TIL) repertoire clonality with response to therapy and to assess the detection of dominant TIL clones within peripheral blood over time in responding patients.
- To investigate the association of whole genome copy number alterations measured on pretreatment archived, formalin fixed, paraffin embedded (FFPE) tumor with response to therapy.

4.0 BACKGROUND & RATIONALE

4.1 Background

4.1.1 Background on RCC and Standard Therapies

RCC is the most common primary malignant tumor of the kidney in adults representing approximately 4% of all adult cancers [1]. RCC is rare in children and young adults, increasing in incidence with age and presenting with a median age at diagnosis of 64 [2]. RCC encompasses a heterogeneous group of tumors subdivided largely by their histologic appearance. The most common histologic types of RCC include clear cell (75% of tumors), papillary (10%), and chromophobe (5%) tumors. Additional rare subtypes of RCC are recognized including medullary, collecting duct, and RCC associated with Xp11 translocation. A pathologic diagnosis of unclassified RCC still accounts for 4-6% of all tumors [3].

Clear cell RCC tumors in both hereditary and sporadic forms are associated with loss of function of the *von Hippel-Lindau* tumor suppressor gene on the short arm of chromosome 3 (3p25.3) as a result of deletion, mutation, or epigenetic silencing [4]. The loss of VHL expression results in the de-regulation of hypoxia-inducible factor (HIF)-1 and -2 transcription factors and constitutive expression of a number of hypoxia-responsive gene products that control angiogenesis, cell cycle, and energy homeostasis. Insight into the abnormal molecular biology common to most clear cell RCC tumors has encouraged the clinical development of novel targeted therapies for this disease directed at signaling pathways affected by *VHL* inactivation. Since 2005, nine new anti-angiogenic drugs have been approved by the FDA for the treatment of advanced RCC. These include oral tyrosine kinase inhibitors (sorafenib, sunitinib, pazopanib,

axitinib, cabozantinib, and lenvatinib) that disrupt vascular endothelial growth factor (VEGF)-receptor and other oncogenic pathway signaling mediated by receptor tyrosine kinases; the VEGF-specific monoclonal antibody (mAb) bevacizumab; and inhibitors of mammalian target of rapamycin (mTOR) (temsirolimus and everolimus). Although these targeted therapies have been rapidly adopted as first and second line treatments for metastatic clear cell RCC, such therapies are fundamentally palliative as development of tumor resistance and disease progression has been a uniform observation. The median time to tumor progression is < 12 months for patients treated with any of these single agents [5-13].

Cumulative evidence suggests that cellular immune responses may play an important role in modulating tumor progression in cancer patients [14]. Specific examples include the documentation of rare spontaneous regressions of RCCs, melanomas, and other tumors [15], identification of naturally occurring T cells recognizing tumor-associated antigens in tumor patients [16, 17], and the positive association of T cell infiltration into tumors with favorable disease outcome in various malignancies [14]. 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.

Such observations have encouraged the development and clinical testing of therapeutic strategies designed to augment tumor-specific T cell responses in cancer patients including vaccines, cytokines, cellular therapies, and most recently immune check point blocking antibodies. Identification and cloning of the genes for IL-2 and interferon-alfa (IFNα) led to the extensive clinical investigation of systemically delivered cytokines for RCC and other tumors beginning in the 1980's. IL-2 and IFNα were sufficiently active against advanced RCC to establish cytokine immunotherapy as standard front line treatment for RCC from the early 1990's to the introduction of targeted agents beginning in 2005 [18].

4.1.2 Interleukin-2 Therapy for Advanced RCC.

Recombinant human IL-2 (aldesleukin), a potent growth and differentiation factor for T and NK cells was first explored as a cancer therapy in the mid 1980's by investigators at the National Cancer Institute (NCI) Surgery Branch and subsequently other institutions. Dose escalation studies identified the highest tolerable doses of IL-2 administered as an IV bolus on an every 8 hour schedule. Treatment with 720,000 U/kg or 600,000 U/kg by IV bolus every 8 hours to tolerance and a maximum of 14 doses on weeks 1 and 3 of a treatment course represented the high dose (HD) IL-2 regimen that received FDA approval for the treatment of metastatic RCC in 1992. Approval was based on pooled results of 255 patients treated as part of seven phase II clinical trials conducted at 21 institutions. Patients received from 1 to 3 courses of therapy in total. The overall objective response rate (ORR) was 14% with 5% complete responders (CRs) [19]. Most remarkable was the durability of CRs following IL-2 therapy. For example, the long term follow-up of 259 RCC patients treated by HD IL-2 at the National Cancer Institute Surgery Branch noted recurrent disease in only 4 of 23 patients (17%) who achieved a CR with a median duration of ongoing CR > 11 years at the time of reporting [20].

Despite acute and severe toxicities associated with administration of HD IL-2 necessitating inpatient and typically ICU-level care, the unique potential to achieve unmaintained CRs in RCC patients has sustained HD IL-2 as a viable first-line treatment option for highly selected RCC

patients even in the face of competition from the more recently available targeted therapies that are delivered in an outpatient setting.

Alternate doses and schedules for IL-2 have also been investigated with the goal of avoiding severe toxicity and potentially the need for inpatient administration. In a moderate size phase II study with 27 RCC patients, subcutaneous (SQ) IL-2 given once daily, 5 days per week for 6 weeks in a fully outpatient setting observed an ORR of 23 % including 8% CR [21]. Investigators at the NCI subsequently conducted a randomized, 3-arm trial to compare HD IL-2 with low dose IL-2 regimens given as SQ dosing 5 days/week for 6 weeks, or 72,000 U/kg by IV bolus on a schedule of every 8 hours administration as for the standardized HD regimen. Although the low dose regimens demonstrated modest anti-tumor activity with ORR's of 10% and 11% for SQ or low dose IV administration respectively, the investigators concluded the HD approach was superior for overall response rate (21%) depth of response (6% CR for HD vs 1-2% for low-dose arms) and durability of response [22].

The Cytokine Working Group also studied standard HD IL-2 versus outpatient SQ IL-2 plus IFNα in a randomized phase III trial. As seen in the NCI trial, HD IL-2 was also found to be superior to the SQ combination of IL-2 and IFNα by ORR (25% vs 12%), depth of response (8% vs 2% CR) and durability of response (median response duration 10 vs 7 months) [23].

The therapeutic index for HD IL-2 could be enhanced by improved selection of patients likely to respond. Retrospective analyses of patient outcomes following HD IL-2 have empirically observed that clear cell RCC tumors are far more responsive than non-clear cell histologies to HD IL-2 [24, 25]. However, predictive markers for IL-2 response among clear cell RCC patients have remained elusive. Selection of clear cell RCC patients suitable for treatment by HD IL-2 is based on clinical parameters that include a good performance status and intact cardiac, pulmonary, and renal function.

4.1.3 PD-1/PD-L1 Pathway and Tumor Immunity

Preclinical studies and results from early phase clinical trials now suggest that resistance mechanisms exploited by tumors may play a dominant role in limiting the effectiveness of T cell mediated cancer therapies [26]. Thus, an emerging and highly promising approach to cancer immunotherapy for advanced RCC and other cancers is antibody-mediated blockade of inhibitory co-receptors expressed on T lymphocytes; or so-called immune checkpoints. Programmed cell death-1 (programmed death-1; PD-1; CD279) is an immune checkpoint receptor emerging as a target for anti-tumor immunotherapy [26]. The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control.

PD-1 was shown to be expressed on activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B-cells, Tregs and Natural Killer cells. The normal function of PD-1 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) [26].

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 [27]. 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. Tumor expression of PD-L1 has been associated with de-regulated oncogene signaling [28, 29], tumor hypoxia [30], and local inflammatory signals including IFN-gamma [31]. A model of tumor up-regulation of PD-L1 expression in response to TIL and local cytokine release as a mechanism to evade effector immune responses has been termed "adaptive resistance" and may represent the most common mechanism for PD-L1 expression in a wide variety of tumor histologies [31]. 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.

Regulatory T cells (Treg) inhibit cellular immune responses and help to maintain self-tolerance. Treg cells express constitutive high levels of several immune checkpoint receptors including CTLA4, PD-1 and others. Rather than exerting inhibitory effects, these receptors appear to enhance Treg activity or proliferation. Thus, separate from their influence on effector T cells, therapeutic antibodies blocking checkpoint receptors may also suppress the activity of Treg cells as an additional mechanism contributing to overall enhanced anti-tumor immunity [26].

The expression of PD-1 pathway proteins has been extensively studied in RCC tumors and shown to closely associate with RCC progression and poor disease specific outcomes. In the largest reported series of 306 clear cell RCC tumors, Thompson and co-workers analyzed PD-L1 expression by immunostaining formalin-fixed paraffin-embedded (FFPE) tissue samples. Tumor cell membranous expression of PD-L1 (with a threshold of $\geq 5\%$ of tumor cells stained with mAb 5H1) was seen in 24% of samples and strongly associated with cancer-specific death (risk ratio (RR) 3.92; $P < 0.001$). This association also remained significant in multivariate modeling (RR 2.0, P=0.003) [32]. PD-1 expression by tumor-infiltrating lymphocytes has also been analyzed in both fresh-frozen or FFPE clear cell RCC tissue. High PD-1 expression associated with distant metastatic relapse, and inferior relapse-free and overall survival versus the PD-1-negative patient subset [33, 34].

The recognition of advanced RCC as a tumor responsive to immunotherapy together with evidence for a PD-1/PD-L1 mediated immune escape mechanism operating in RCC tumors has provided a compelling rationale for initial testing of blocking antibodies specific for PD-1 or PD-L1 in patients with advanced RCC. Nivolumab, a fully human IgG4 mAb specific for human PD-1 was tested in a dose escalation format in 296 patients that included 34 patients with advanced clear cell RCC treated at 1 or 10 mg/kg every 2 weeks [35]. In this heavily pre-treated cohort, significant anti-tumor activity was observed with an ORR of 27% and median duration of response 12.9 months. Treatment was judged to be generally well tolerated and no MTD was reached. Grade 3/4 treatment related adverse events were observed in 14% of patients and there were 3 drug-related deaths due to pneumonitis, however none in the RCC cohort [35]. In a phase II study, nivolumab was further studied in 168 RCC patients randomized to nivolumab at 0.3, 2

or 10 mg/kg every 3 weeks. ORR by treatment group was 20%, 22% and 20% respectively and the overall rate of treatment related AE's was 11%. There were no high-grade pneumonitis events and no treatment related deaths. There was no dose-response relationship detected for ORR, PFS, or incidence of treatment-related AE's [36]. A phase III study of nivolumab (Checkmate 025) enrolled 821 RCC patients who had failed 1 to 3 lines of prior therapy including antiangiogenic treatment targeting the VEGF pathway. Nivolumab given at 3 mg/kg every 2 weeks was compared to everolimus in 1:1 randomization. Median overall survival favored nivolumab (HR 0.73, P=0.002) and the survival benefit for nivolumab treatment was seen independent of tumor expression of PD-L1. The ORR determined by RECIST 1.1 was also superior for nivolumab (25% vs 5%). There were no nivolumab associated deaths, and the incidence of grade 3/4 treatment-related AE's was lower with nivolumab than everolimus (19% vs 37%). [37]

Two blocking mAb's targeting PD-L1 have also reported results from phase I clinical trials that included patients with advanced RCC. Both BMS-936559 and MPDL3280A were judged to be well tolerated and demonstrated ORR's of 12% and 14% respectively in heavily pre-treated RCC patients [38, 39].

Taken together, the emerging data with blocking antibodies targeting PD1 or PD-L1 demonstrating spontaneous and durable regressions for a subset of treatment-refractory RCC tumors suggests the PD-1 pathway represents a dominant control point for the regulation of tumor-reactive T cell responses.

4.1.4 Preclinical and Clinical Trial Data for Pembrolizumab

Pembrolizumab is a potent and highly selective humanized monoclonal antibody (mAb) of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Pembrolizumab has been studied in an open-label, single-arm, phase 2 trial (Keynote 427) as first-line, single-agent therapy for RCC patients with both clear cell (cohort A; N=110) and non–clear cell histology (cohort B; N=165) [40, 41]. With a median follow up of 18.5 months, patients treated in Cohort A had a confirmed ORR of 36% and a median OS that has not been reached. The incidence of grade 3-5 treatment-related AE's was 29% [40].Refer to the Investigator's Brochure for additional pembrolizumab preclinical and clinical data. Keytruda™ (pembrolizumab) is approved in the United Stated for the treatment of patients with advanced RCC (in combination with axitinib) and 14 additional cancer indications.

4.1.5 Immune Checkpoint Antibody Combination Therapy for Advanced RCC

The generally favorable safety profile for blocking antibodies targeting PD1 or PD-L1 has encouraged exploration of novel combinations incorporating these agents. Nivolumab has been studied in combination with the anti-cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) antibody, ipilimumab, versus sunitinib in the front-line setting in a randomized, phase 3 trial for patients with advanced, clear cell RCC (Checkmate 214). In the primary analysis population of 847 patients with intermediate or poor risk disease by International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) criteria, ipilimumab plus nivolumab demonstrated a superior median OS that was not reached versus 26.0 months with sunitinib (hazard ratio for death, 0.63; P<0.001). A superior ORR was observed with ipilimumab plus nivolumab versus

sunitinib (42% vs 27%; p<0.001) with a CR rate of 9% vs 1%, respectively. Grade 3/4 treatment-related adverse events occurred in 46% of nivolumab plus ipilimumab treated patients versus and 63% of sunitinib treated patients [42]. Based on these data, ipilimumab plus nivolumab received FDA-approval in April 2018 for treatment of intermediate and poor risk, previously untreated advanced RCC patients.

Pembrolizumab has been studied in combination with axitinib, a VEGF-receptor selective TKI, in the front-line setting in a randomized phase 3 trial enrolling 861 patients with advanced clear cell RCC (Keynote 426). After a median follow-up of 12.8 months, the estimated OS at 12 months favored pembrolizumab–axitinib versus sunitnib (89.9% vs 78.3%; hazard ratio for death, 0.53; P<0.0001). Median progression-free survival (PFS) also favored pembrolizumab-axitinib (15.1 months vs 11.1 months; hazard ratio for disease progression or death, 0.69, P<0.001). The ORR was 59% in the pembrolizumab–axitinib group and 36% in the sunitinib group (P<0.001). The OS and PFS benefit of pembrolizumab plus axitinib was observed across all IMDC risk groups. Grade 3/4 treatment-related adverse events occurred in 62.9% of pembrolizumab-axitinib treated patients versus and 58.1% of sunitinib treated patients [43]. Based on these data, pembrolizumab plus axitinib received FDA-approval in April 2019 for the first-line treatment of patients with advanced RCC.

The anti-PDL1 antibody avelumab has also been studied in combination with axitinib in the front-line setting in a randomized phase 3 trial enrolling 886 patients with advanced clear cell RCC (Javelin 101). In the primary analysis population of 560 patients with PD-L1–positive tumors (63.2%), the median progression-free survival was 13.8 months with avelumab-axitinib versus 7.2 months with sunitinib (hazard ratio for disease progression or death, 0.61, P<0.001); and the ORR was 55.2% with avelumab plus axitinib versus 25.5% with sunitinib. In the overall population, the median PFS for pembrolizumab-axitinib was 13.8 months, as compared with 8.4 months for sunitinib (hazard ratio, 0.69, P<0.001) and PFS favored pembrolizumab-axitinib across all IMDC risk groups. Grade ≥3 treatment-related adverse events occurred in 56.7% of avelumab-axitinib treated patients versus and 55.4% of sunitinib treated patients [44]. Based on these data, avelumab plus axitinib received FDA-approval in May 2019 for first-line treatment of patients with advanced RCC.

In summary, treatment regimens containing blocking antibodies targeting PD1, CTLA-4 or PDL1 are now firmly established as front-line standard of care treatment options for most patients with advanced RCC.

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

Several preclinical and clinical observations support testing of the combination of IL-2 with pembrolizumab for patients with advanced clear cell RCC. Recently, pretreatment tumor expression of PD-L1 was associated with response to HD IL-2 therapy [25]. In addition, high numbers of intratumoral Treg have been associated with poor survival for RCC patients treated with low- or intermediate-dose IL-2 [45]. These data suggest that PD-1 pathway blockade may disrupt counter-regulatory mechanism that limit the anti-tumor activity of IL-2 therapy in RCC patients.

The combination of IL-2 with PD-1 pathway blockade has been explored in a preclinical model of chronic viral infection and T cell exhaustion. In the murine chronic lymphocytic choriomengitis virus infection model, IL-2 synergized with PD-1 pathway blockade enhancing virus-specific CD8+ T cell responses and deceasing viral load. IL-2 proved more potent in this model than combining check point blocking antibodies targeting LAG-3 or TIM3 with anti-PD-L1 or co-blockade of IL-10R and PD-L1 [46].

In a pilot study at the NCI, HD IL-2 was combined with the anti-CTLA4 mAb ipilimumab in melanoma patients. Both drugs were able to be given at full doses without encountering dose limiting toxicity supporting the feasibility of developing combination therapy with immune checkpoint blockade and HD IL-2 [47]. Long-term follow-up of the patients in this study has suggested synergistic anti-tumor activity with 6/36 (17%) melanoma patients achieving CR [48].

In a single-institution, single-arm study, patients with metastatic clear cell RCC were treated with pembrolizumab monotherapy x 3 cycles followed by pembrolizumab plus high dose bolus IL-2 delivered on a 5 dose per week schedule. No treatment-limiting toxicity was encountered. Objective responses were observed in 20/26 patients (77%) including 3 CR (12%) [49].

4.2.2 Hypothesis for Combination Therapy

The immune checkpoint receptor PD-1 and associated ligand PD-L1 may represent a dominant mechanism for RCC resistance and escape from immune surveillance and from anti-tumor effects mediated by IL-2. Targeting PD-1 with the blocking mAb pembrolizumab in combination with IL-2 will result in a higher frequency and/or greater depth of anti-tumor effects in comparison to the historical experience with anti-PD1 or IL-2 monotherapy in untreated or in treatment-refractory patients.

4.2.3 Rationale for Dose Selection/Regimen/Modification

4.2.3.1 Rationale for Pembrolizumab Dose Selection

The planned dose of pembrolizumab for this study is 200 mg every 3 weeks (Q3W). Based on the totality of data generated in the Keytruda development program, 200 mg Q3W is the appropriate dose of pembrolizumab for adults across all indications and regardless of tumor type. As outlined below, this dose is justified by:

- Clinical data from 8 randomized studies in melanoma and NSCLC indications demonstrating flat dose- and exposure-efficacy relationships from 2 mg/kg Q3W to 10 mg/kg Q2W, representing an approximate 5- to 7.5-fold exposure range (refer to IB, Section 5.2.2)
- Population PK analysis showing that both fixed dosing and weight-based dosing provides similar control of PK variability with considerable overlap in the distributions of exposures, supporting suitability of 200 mg Q3W
- Clinical data showing meaningful improvement in benefit-risk including overall survival at 200 mg Q3W across multiple indications, and

- Pharmacology data showing full target saturation in both systemic circulation (inferred from pharmacokinetic [PK] data) and tumor (inferred from physiologically-based PK [PBPK] analysis) at 200 mg Q3W

4.2.3.2 Rationale for IL-2 Dose Selection

IL-2 dosing will follow a 3+3 dose escalation scheme. The starting Dose Level 1 will be 250,000 U/kg/dose delivered SQ daily 5 days/week in the first week and then 125,000 U/kg/dosed daily 5 days/week during the next 5 weeks as reported by investigators at the NCI [22]. The toxicity of low dose, SQ administered IL-2 is greatly reduced versus HD IV bolus dosing allowing a greater safety margin for assessing toxicity for IL-2 in combination with pembrolizumab. This Dose Level also derives practical advantage for a fully outpatient treatment regimen.

For dose escalation, IL-2 will convert to IV bolus dosing requiring inpatient administration. At dose Level 2, patients will be treated by a low dose IV bolus regimen of 72,000 U/kg/dose IV every 8 hours to a maximum of 14 doses in 2 cycles per treatment course starting on day 2 and day 23 [22]. At Dose Level 3, patients will receive HD bolus dosing of 600,000 U/kg/dose IV every 8 hours to a maximum of 14 doses in 2 cycles per course starting on day 2 and day 23 representing a conventional HD IL-2 treatment approach with cycle 2 dosing adjusted to follow pembrolizumab administered on day 22. Recognizing there is practice heterogeneity in the delivery of HD IL-2, a two week (rather than 1 week) recovery period following cycle 1 treatment is a standard approach at some treatment centers [50]. A 12 week treatment course for HD IL-2 is the standard convention of the Cytokine Working Group [25].

4.2.4 Rationale for Endpoints

4.2.4.1 Primary Endpoint - Safety

The primary objective of this trial is to characterize the safety and tolerability of pembrolizumab in combination with IL-2 in subjects with advanced clear cell RCC. The safety analysis will be based on subjects who experience toxicities as defined by CTCAE v5.0 criteria. Safety will be assessed by quantifying the toxicities and laboratory abnormalities by grades experienced, including any serious adverse events (SAEs). Furthermore, potential immune-related adverse events (irAEs) will be collected and designated as immune-related events of clinical interest (ECIs) as described in Section 7.3.3.2. The attribution to study drugs, time-of-onset, duration of the event, its resolution, and any concomitant medications administered will be recorded.

4.2.4.2 Secondary Endpoint - Efficacy

The efficacy objective of this trial is to evaluate the anti-tumor activity of pembrolizumab plus IL-2 in subjects with advanced RCC. Responses will be evaluated by RECIST 1.1. Best overall response rate (ORR) to include complete responders (CR) and partial responders (PR); disease control rate (DCR = CR+PR+stable disease, SD), and progression free survival (PFS) for patients treated with IL-2 combined with pembrolizumab will be collected and analyzed by cohort and for all treated patients. Outcomes will be compared to historical data for RCC patients treated with IL-2 or anti-PD-1 as monotherapy.

Immunotherapeutic agents may produce antitumor effects by potentiating endogenous cancer-specific immune responses which may be functionally anergic. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents, and can manifest a clinical response after an initial increase in tumor burden or even the appearance of new lesions. In subjects who have initial evidence of radiological PD following a first course of treatment, it is at the discretion of the investigator whether to continue a subject on study treatment for a second treatment course. This decision should be based on the clinical judgment of the subject's overall clinical condition, including performance status, clinical symptoms, laboratory data, and tolerance for study treatments.

Subjects recommended to receive a second treatment course after PD should meet the following criteria:

- Absence of signs and symptoms indicating disease progression
- Absence of progressive tumor at critical anatomical sites (e.g., cord compression) requiring urgent alternative medical intervention
- Absence of rapid progression of disease
- No decline in ECOG performance status

This allowance takes into account the observation that some subjects can have a transient tumor flare in the first few months after the start of immunotherapy, but with subsequent disease response.

4.2.4.3 Exploratory Endpoints - Biomarker Research

4.2.4.3.1 Pretreatment Tumor PD-L1 Expression

Responses to both IL-2 and to PD-1 pathway blocking mAb have been shown to be associated with PD-L1 expression on pretreatment RCC tumor cells [25, 36, 39] which may reflect the presence of a pre-treatment tumor-reactive adaptive immune response [51]. Thus, PD-L1 represents a potential biomarker for tumor response to the combination of IL-2 and pembrolizumab. FFPE archival or newly obtained tumor biopsy will be submitted to the central vendor for IHC analysis of PD-L1 expression.

4.2.4.3.2 Regulatory T Cell Frequency in Peripheral Blood and the Tumor Microenvironment.

As observed in other tumor histologies, increased numbers of Tregs ($CD4^{+}/CD25^{high}/FOXP3^{+}$) are found in peripheral blood and TIL populations in RCC patients and are associated with adverse patient outcomes [52]. Tregs constitutively express IL-2 receptors and expand in response to IL-2 therapy representing a potential mechanism of tumor resistance to IL-2 treatment. Quantitatively higher numbers of intratumoral Treg have been associated with poor survival for RCC patients treated with low- or intermediate-dose IL-2 [45]. Tregs express high levels of several immune checkpoint receptors including CTLA4, PD-1 and others. Rather than exerting inhibitory effects, these receptors appear to enhance Treg activity or proliferation. Thus, separate from their influence on effector T cells, therapeutic antibodies blocking checkpoint receptors may suppress the activity of Treg cells as an additional mechanism contributing to overall enhanced anti-tumor immunity [53]. Absolute numbers of Treg and the

Treg:Teff ratios in peripheral blood and TIL will be assessed at baseline and during therapy. Analyses of T cell subsets will be correlated with clinical outcomes.

4.2.4.3.3 *De Novo* Immune Responses Targeting the Ubiquitous RCC Antigen 5T4.

Detection of *de novo* serological and/or T cell responses specific for melanoma tumor antigens such as NY-ESO-1 likely represents on-target activity of immune check point blocking antibodies and is associated with favorable clinical outcomes in melanoma patients treated by ipilimumab [54, 55]. However, RCC does not commonly express $CD8^+$ CTL-defined tumor antigens encoded by cancer-testis gene families (*MAGE, BAGE, GAGE, or NY-ESO-1*) frequently expressed in other tumor histologies [56].

The 5T4 antigen is a cell surface glycoprotein expressed on many common epithelial tumors including 95% of primary RCC's and is highly expressed on placental trophoblast cells, but is not detected on most other normal tissues. A higher frequency of 5T4 expression has been associated with more advanced disease in patients with cervical, colorectal (CRC), ovarian, gastric, and non-small cell lung cancers (NSCLC) [57]. 5T4 expression on NSCLC tumor-initiating cells and by putative RCC tumor-initiating cells has also been recently described [58, 59].

The development of *de novo* 5T4 specific humoral and/or cellular immune responses during and following treatment of RCC patients with IL-2 plus pembrolizumab will be analyzed as a potential marker of "on target" effective anti-tumor immunity and correlated with clinical response.

4.2.4.3.4 T Cell Receptor Repertoire Clonality in RCC TIL and Persistence of Dominant Clones in the Peripheral Blood of Responding Patients

The array of potential tumor antigens including tumor mutation-specific neoantigens recognized by tumor-reactive T cells in RCC patients responding to immunotherapy with IL-2 or PD-1 pathway specific agents is not well understood. In addition, techniques to facilitate antigen identification in a clinically relevant time frame are also presently lacking.

The application of high-throughput, quantitative sequencing applied to the T cell receptor (TCR) β chain CDR3 domains derived from complex T cell populations may yield a practical bioassay revealing T cell clonal expansions and thereby identifying an ongoing adaptive immune response within the tissue compartment that has been sampled. Recently, such an approach was applied to analyze TIL within the tumor microenvironment of melanoma patients treated with pembrolizumab. This study observed that a low TIL clonality phenotype was strongly associated with disease progression [51].

A similar sequencing analysis will be undertaken using pre-treatment archived RCC tumor. The resulting TIL clonality score will then be correlated with clinical outcomes of RCC patients treated with IL-2 plus pembrolizumab. Further, each unique TCRβ CDR3 sequence derived from an expanded TIL clone represents a screening tag that can be used to analyze other biological samples. The presence/persistence of TIL-associated dominant clones detected within peripheral blood sampled over time on therapy will be associated with tumor response or progression.

4.2.4.3.5 The Association of Chromosomal Copy Number Alterations with Response to Therapy

Gain-of-function oncogene mutations are rarely identified in whole-exome or whole-genome sequencing derived data sets for ccRCC tumors [60]. As a consequence, targeted gene-sequencing based diagnostic panels have not made inroads into the clinical management of ccRCC patients. In contrast, metastatic ccRCC tumors frequently contain large scale chromosomal abnormalities representing irreversible genetic derangements that can be readily identified by cytogenetic or array-based comparative genomic hybridization technologies [61, 62]. Deletion of 3p is detected in the majority of ccRCC tumors and spans the Von Hippel Lindau (VHL) tumor suppressor gene at 3p21. Additional common chromosomal abnormalities include gains (5q, 7) and losses (3p, 14q, 8p, 6q, 9p, 4p, and Y in males) occurring in > 10% of ccRCC tumors [61]. A subset of these chromosomal lesions (loss of 9p, 14q, and gain of 8q) represent independent poor prognostic markers for disease-specific survival [63-65].

Hypothesis: Subsets of ccRCC tumors defined by common chromosomal gains or losses will have different response rates to combination immunotherapy with IL-2 and pembrolizumab.

Until recently, cytogenetic or array-based tumor genomic analyses required fresh tumor or frozen tissue specimens respectively, for analysis. The OncoScan (Affymetrix, Santa Clara, CA) array platform is optimized for whole genome analysis of DNA isolated from formalin-fixed paraffin-embedded (FFPE) tissue. The ability to collect whole genome chromosomal CNA data retrospectively from FFPE tumor tissue now allows for directed analysis of patient cohorts receiving a common treatment to correlate genomic phenotypes with clinical outcomes. OncoScan chromosomal array analyses will be carried out on archived tumor for RCC patients treated with IL-2 and pembrolizumab and chromosomal CNAs correlated to objective response rate.

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Subject Inclusion Criteria

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

1. Be willing and able to provide written informed consent for the trial.
2. Be ≥ 18 years of age on day of signing informed consent.
3. Have histologic confirmation of RCC with a clear cell component.
4. Have advanced (not amenable to potentially curative surgery) or metastatic RCC.
5. May have received previous systemic treatments or regimens for metastatic RCC. Prior therapy can include checkpoint blocking antibodies targeting PD-1, PD-L1, or cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) and/or targeted agents including TKIs, mTOR inhibitors, or bevacizumab. Patients may choose to receive study treatment as their initial therapy.
6. Previously treated patients must have documented disease progression after their last line of therapy.
7. Have measurable disease based on RECIST 1.1.
8. Available tissue from an archival tissue sample or newly obtained core or excisional biopsy of a tumor lesion.
9. Have a performance status of 0 or 1 on the ECOG Performance Scale.
10. Demonstrate adequate organ function as defined in Table 2. All screening labs should be performed within 14 days of treatment initiation.

Table 2 Adequate Organ Function Laboratory Values

System	Laboratory or Study Value
Hematological	
Absolute neutrophil count (ANC)	≥1,500 /mcL
Platelets	≥100,000 / mcL
Hemoglobin	≥9 g/dL or ≥5.6 mmol/L
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** ≥40 mL/min for subject with creatinine levels > 1.5 X institutional ULN
Hepatic	
Serum total bilirubin	≤ 1.5 X ULN **OR**
	Direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 X ULN **OR** ≤ 5 X ULN for subjects with liver metastases
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT)[b] Activated Partial Thromboplastin Time (aPTT)[b]	≤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
Pulmonary	
Pulmonary Function Testing[c]	FEV1 and FVC ≥ 65% of predicted
Cardiac	
LV function[c]	LVEF ≥ 50% measured by MUGA scan, echo, or stress test study with myocardial perfusion imaging
Myocardial ischemia screening[c]	Normal/negative cardiac stress testing with myocardial perfusion imaging. **OR** Cardiac catheterization with non-significant angiogram findings reviewed by a Cardiology consultant
[a]Creatinine clearance should be calculated by Cockcroft-Gault [b]Dose Level 2 and 3 patients only. [c]Testing performed prior to study screening are allowable. Pre-treatment testing must have been completed within 6 months of start of treatment.	

11. Female subject of childbearing potential should have a negative urine or serum pregnancy test 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.

12. Female subjects of childbearing potential should be willing to use 2 methods of birth control or abstain from heterosexual activity for the course of the study through 140 days after the last dose of study medication (reference sections 5.5.2 and 13.5). Subjects of childbearing potential are those who have not been surgically sterilized or have not been free from menses for > 1 year.

13. Male subjects who are not surgically sterile and have a female partner of childbearing potential should agree to use an adequate method of contraception or abstain from

heterosexual activity starting with the first dose of study therapy through 200 days after the last dose of study therapy (reference sections 5.5.2 and 13.5).

5.1.2 Subject Exclusion Criteria

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

1. Has received prior therapy with IL-2 or other investigational systemic cytokine therapy signaling through a common γ-chain cytokine receptor including IL-7, IL-15 or IL-21.

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

3. Has had a prior monoclonal antibody within 4 weeks prior to study Day 1. Has had prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to study Day 1

4. Adverse events due to prior treatment must be resolved to ≤ Grade 1.

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

5. For patients previously treated with checkpoint blocking antibodies, no history of myocarditis, pneumonitis or nephritis of any grade associated with the prior treatment.

6. Has had autoimmune toxicity associated with prior checkpoint blocking antibodies requiring more than one drug class of immune suppressive therapy to resolve (e.g. steroid-refractory toxicity requiring infliximab, mycophenolate mofetil, tacrolimus or other immune suppressive agent) or requiring continuous immune suppression > 12 weeks, or having a severity judged to be life threatening by the investigator.

7. Has a known additional malignancy that is progressing or requires active treatment. Exceptions include locally curable cancers such as basal cell carcinoma of the skin, squamous cell carcinoma of the skin, superficial bladder cancer, or carcinoma in situ of the cervix or breast that has undergone potentially curative therapy.

8. Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis.

    - (Dose Level 1) 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.

- (Dose Level 2 and 3) subjects may not have any history of or current CNS metastases. Baseline imaging of the brain is required within 28 days prior to the start of study treatments.

9. 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.

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

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

12. Ongoing symptomatic cardiac dysrhythmias, uncontrolled atrial fibrillation, or prolongation of the corrected QT interval defined as > 450 msec for males and > 470 msec for females.

13. History of any of the following cardiovascular conditions within 6 months of enrollment: cardiac angioplasty or stenting, myocardial infarction, unstable angina, coronary artery bypass graft surgery, class III or IV congestive heart failure as defined by the New York Heart Association, symptomatic peripheral vascular disease, cerebrovascular accident, or transient ischemic attack.

14. Has an active infection requiring systemic therapy.

15. 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.

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

17. 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.

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

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

20. Has received a live vaccine or live-attenuated vaccine within 30 days prior to the first dose of trial treatment. Administration of killed vaccines are allowed.

Note: Seasonal influenza vaccines for injection are generally inactivated flu vaccines and are allowed.

5.2 Trial Treatments

The treatments to be used in this trial are outlined below in Table 3

Table 3 Trial Treatment

Drug	Dose/ Potency	Dose Frequency	Route of Delivery	Regimen/Treatment Period	Use
pembrolizumab	200 mg	Q3W	IV infusion	4 cycles per course	Experimental
Aldesleukin	250,000 or 125,000 U/kg	Daily 5days/7	SQ	1 six-week cycle per course	Non-Standard Dose and Schedule
Aldesleukin	72,000 U/kg	Q8 hrs x 14 doses	IV	2 cycles per course	Non-Standard Dose
Aldesleukin	600,000 U/kg	Q8 hrs x 14 doses	IV	2 cycles per course	Standard
The pembrolizumab dosing interval may be increased due to toxicity as described in Section 5.2.1.2.					

5.2.1 Dose Selection/Modification

5.2.1.1 Dose Selection

The rationale for selection of doses to be used in this trial is provided in Section 4.0 – Background and Rationale.

5.2.1.2 Rules for Dose Escalation

Dose-limiting toxicities (DLT's) observed in course 1 will be used to determine escalation to the next dose level. A course is 12 weeks. The study will use a 3 + 3 trial design for IL-2 dose escalation. The first 3 patients will be enrolled at Dose Level 1. If no dose-limiting toxicities (DLT's) occur in the first 3 patients over treatment course 1, Dose Level 2 will then open for enrollment of the next 3 patients. In the absence of DLT's in three patients treated at Dose Level 2, then Dose Level 3 will open for enrollment of the next 3 patients.

If 1 of 3 subjects in a cohort experiences a DLT, the Cohort will expand to 6 pts. If only 1 of 6 patients experiences a DLT with all patients followed for safety endpoints to the end of course 1, then the next cohort dose level will open to enroll.

If two or more patients in a cohort experience a DLT, that dose level exceeds the MTD.

If two or more delayed DLT's (i.e., DLT's that occur after course 1) are noted within a dose-escalation cohort, accrual will be held pending safety analysis by the Principal Investigator and Merck and restarted only with Principal Investigator and Sponsor approvals with IRB and FDA notification.

Dose escalations or de-escalations of pembrolizumab are not allowed. Treatment delays for toxicity are allowable as described in Section 5.2.1.4. Patients enrolled into Dose Level 3 who require treatment interruption and meet restarting criteria as described in Section 5.2.1.4 may have IL-2 dosing de-escalated to the IV IL-2 Dose Level 2 for the subsequent treatment cycle and/or course(s) 2 and/or 3. Individual patient IL-2 dosing cannot be escalated.

5.2.1.3 Definition of Dose-Limiting Toxicities

All toxicities will be graded using the National Cancer Institute (NCI) CTCAE v5.0 (Appendix 2; Section 13.2). Dose-limiting toxicity (DLT) assessment will be based on events occurring during the DLT assessment period, which is defined as course 1. Dose-limiting toxicities include all adverse experiences that are clearly not related to disease progression or intercurrent illness if judged by the investigator to be possibly, probably, or definitely related to study treatments that meet or exceed the following severity criteria:

- Toxicities associated with pembrolizumab representing autoimmune phenomenon have been extensively characterized, and may be exacerbated by combination treatment with IL-2. Treatment associated AE's that represent immune mediated pathology are codified in Section 5.2.1.4, Table 4. For patients at Dose Level 1, all AE's resulting in Guideline recommendation for Treatment Discontinuation will also constitute a DLT.

- A delay in the scheduled administration of either component of therapy of > 21 days for pembrolizumab or SQ or IV bolus IL-2.

- Bolus IV dosing of IL-2 (Dose Level 2 and 3), especially at Dose Level 3, is known to be associated with acute severe toxicities. Doses are administered to patient tolerance according to established treatment guidelines (Appendix 4, Section 13.4). Toxicities associated with IL-2 administration will be initially managed according to the IL-2 Toxicity Management Guidelines (Appendix 4, Section 13.4). Toxicities that fail to stabilize within 48 hours of the last IL-2 dose or that fail to show improvement within 72 hours of the last IL-2 dose will convert to management according to Section 5.2.1.4, Table 4 and resulting AE grade and Treatment Discontinuation assignment forming the basis for DLT determination.

- Grade 5 toxicity

5.2.1.4 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 drug-related toxicities and severe or life-threatening AEs as per Table 4 below. See Section 5.4.1 and Events of Clinical Interest Guidance Document for supportive care guidelines, including use of corticosteroids.

Dose escalations or de-escalations of pembrolizumab are not allowed.

SQ IL-2 must be withheld for drug-related toxicities and severe or life-threatening AEs as per Table 4 below. SQ IL-2 associated with AE's requiring treatment interruption can be restarted at a reduced dose not lower than a 50% reduction of the recommended 125,000 U/kg dose.

If possible, the Investigator may attribute each toxicity event to pembrolizumab or IL-2 alone with a resulting dose modification applied to a single study drug. For example, local IL-2 injection site reaction could result in a hold of SQ IL-2 dosing with pembrolizumab continued without interruption.

Patients enrolled into Dose Level 3 who require treatment interruption and meet restarting criteria as described in Table 4 may have IL-2 dosing de-escalated to Dose Level 2 for the subsequent treatment cycle or course(s). Individual patient IL-2 dosing cannot be escalated.

Table 4 Dose Modification Guidelines for Drug-Related Adverse Events

General instructions:

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

Immune-related AEs	Toxicity grade or conditions (CTCAEv5.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus). • Participants with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

AST / ALT elevation or Increased bilirubin	Grade 2	Withhold	• Administer corticosteroids (initial dose of 0.5- 1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable)
	Grade 3 or 4	Permanently discontinue	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold	• Initiate insulin replacement therapy for participants with T1DM • Administer anti-hyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes.
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated.	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hyperthyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hypothyroidism	Grade 2-4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care	• Monitor for signs and symptoms of thyroid disorders.
Nephritis and Renal dysfunction	Grade 2	Withhold	• Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper.	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Neurological Toxicities	Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Asymptomatic Troponin Elevation	Withhold	• Consider corticosteroids	• Repeat and monitor troponin • Consider Cardiology consultation for further diagnostic workup
	Grade 2	Permanently discontinue	• Administer corticosteroids (prednisone 2 mg/kg or equivalent)	• Hospitalization • Urgent cardiology consultation for evaluation and management • Taper steroid over at least 1 month with close monitoring • Repeat cardiac MRI post treatment
	Grade 3 or 4	Permanently discontinue	• Immediate initiation of corticosteroids (prednisone 2 mg/kg or equivalent or 1 g IV bolus) • Consider adding second immunosuppressive agent	• Hospitalization to intensive cardiac care unit • Emergent cardiology consultation for evaluation and management • Taper steroid over at least 1 month with close monitoring • Repeat cardiac MRI post treatment

Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Confirmed SJS, TEN, or DRESS	Permanently discontinue		
All other immune-related AEs	Intolerable/ persistent Grade 2	Withhold	• Based on type and severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3	Withhold or discontinue based on the type of event.		
	Grade 4 or recurrent Grade 3	Permanently discontinue		

AE(s)=adverse event(s); ALT= alanine aminotransferase; AST=aspartate aminotransferase; CTCAE=Common Terminology Criteria for Adverse Events; DRESS=Drug Rash with Eosinophilia and Systemic Symptom; GI=gastrointestinal; IO=immuno-oncology; ir=immune related; IV=intravenous; SJS=Stevens-Johnson Syndrome; T1DM=type 1 diabetes mellitus; TEN=Toxic Epidermal Necrolysis; ULN=upper limit of normal.

[1]**NOTES:**

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

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

5.2.2 Timing of Dose Administration

Trial treatment should begin on Day 1 of each cycle after all procedures/assessments have been completed as detailed on the Trial Flow Chart (Section 6.0).

All pembrolizumab treatments will be administered on an outpatient basis.

Pembrolizumab 200 mg will be administered as a 30 minute IV infusion every 3 weeks (±2 days, see Section 6.0). Every effort should be made to target infusion timing to be as close to 30 minutes as possible. 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).

IL-2 administration will follow pembrolizumab dosing for all cohorts. Outpatient SQ IL-2 doing will begin on cycle day 1 after completion of the pembrolizumab infusion. For day 1 cycle 1, patients should be observed ≥ 1 hour after completion of pembrolizumab before the first SQ IL-2 dose.

Patients will be admitted on cycle day 2 (or the next available ICU admission day) to begin IV IL-2 treatments for Cohorts 2 and 3.

5.2.3 Trial Blinding/Masking

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

5.3 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 medications or vaccinations specifically prohibited during the trial, discontinuation from trial therapy 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 or the Principal Investigator.

5.3.1 Acceptable Concomitant Medications

All treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the case report form (CRF) including all prescription, over-the-counter (OTC), herbal supplements, and IV medications 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 for the treatment of preexisting conditions in use immediately prior to the start of study treatment and/or up to 30 days after the last dose of trial treatment should also 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 7.3.

5.3.2 Prohibited Concomitant Medications

Subjects are prohibited from receiving the following therapies during the Screening, Treatment, and Follow-Up phases of this trial:

- Anti-cancer 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 after consultation with Principal Investigator.
- 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, chicken pox, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus

vaccines and are allowed; however intranasal influenza vaccines (e.g. Flu-Mist®) are live attenuated vaccines, and are not allowed.

- 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 Principal Investigator.

Subjects who, in the assessment by the investigator or Principal 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.

5.4 Rescue Medications & Supportive Care

5.4.1 Supportive Care Guidelines

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

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

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

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

- For **Asymptomatic Troponin Elevation**, repeat and monitor troponin. Perform further diagnostic workup; ECG, cardiac MRI and consider Cardiology consultation. Consider corticosteroids if troponin doesn't normalize.
- For **Grade 2 events**, hospitalize patients to expedite Cardiology consultation and evaluation.
  - Troponin and BNP; ECG and continuous cardiac monitoring; Echocardiogram and Cardiac MRI.
  - Administer prednisone or equivalent at 2 mg/kg.
  - Upon recovery, taper steroids over at least 1 month with close monitoring by lab testing and new symptoms. Repeat cardiac MRI post treatment.
- For **Grade 3-4 events**, hospitalize to intensive cardiac care unit with heart failure therapy as needed. Emergent Cardiology evaluation
  - Troponin and BNP; ECG and continuous cardiac monitoring; Echocardiogram and Cardiac MRI.
  - Myocardial biopsy if feasible
  - Immediate initiation of immunosuppression with prednisone or equivalent at 2 mg/kg or 1 g IV bolus. Consider adding a second immunosuppressive agent, such as ATG
  - Upon recovery, taper steroids over at least 1 month with close monitoring by lab testing and new symptoms. Repeat cardiac MRI post treatment.

- **Diarrhea/Colitis**:

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

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

- **Type 1 diabetes mellitus (if new onset, including diabetic ketoacidosis [DKA]) or ≥ Grade 3 Hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis (DKA)**
  - For **T1DM** or **Grade 3-4** Hyperglycemia

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

- **Hypophysitis**:
    - For **Grade 2-4** 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.

- **Hyperthyroidism or Hypothyroidism**:

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

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

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

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

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

  Table 5 below shows treatment guidelines for subjects who experience an infusion reaction associated with administration of pembrolizumab.

Table 5 Infusion Reaction Treatment Guidelines

NCI CTCAE v5.0 Grade	Treatment	Premedication at subsequent dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for < =24 hrs	**Stop Infusion and monitor symptoms.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. **Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.**	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic).
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **Subject is permanently discontinued from further trial treatment administration.**	No subsequent dosing
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.		

5.5 Diet/Activity/Other Considerations

5.5.1 Diet

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

5.5.2 Contraception

Pembrolizumab or IL-2 may have adverse effects on a fetus in utero. Furthermore, it is not known if pembrolizumab or IL-2 have transient adverse effects on the composition of sperm.

- Non-pregnant, non-breast-feeding women of childbearing potential (WOCBP) may be enrolled if they are abstinent from penile-vaginal intercourse or if they are willing to use 2 methods of birth control (see section 13.5) for the duration of the study period up to 140 days after the last dose of pembrolizumab.

- Male participants with female partners of childbearing potential are eligible if they are abstinent from penile-vaginal intercourse or they and their partner(s) agree to use of 2 methods of birth control (see section 13.5) for the duration of the study period up to 200 days after the last dose of pembrolizumab.

5.5.3 Use in Pregnancy

If a subject inadvertently becomes pregnant while on treatment with pembrolizumab, the subject will immediately be removed from the study. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the Principal Investigator and to Merck without delay and within 24 hours 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 Principal Investigator and to Merck and followed as described above and in Section 7.3.2.

5.5.4 Use in Nursing Women

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

5.6 Subject Withdrawal/Discontinuation Criteria

Subjects may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn by the investigator or the Principal Investigator 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 7.2.4 – Other Procedures.

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

- The subject withdraws consent.
- Confirmed radiographic disease progression

  Note: A subject may be granted an exception to continue on treatment with confirmed radiographic progression if clinically stable or clinically improved, please see Section 5.7
- Unacceptable adverse experiences as described in Section 5.2.
- Intercurrent illness that prevents further administration of treatment
- Investigator's or Principal Investigator's decision to withdraw the subject
- The subject has a confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements
- The subject is lost to follow-up
- Administrative reasons

The End of Treatment and Follow-Up visit procedures are listed in Section 6 (Protocol Flow Chart) and Section 7.2.5 (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 7.3.3.1). Subjects who discontinue for reasons other than progressive disease will have post-treatment Surveillance 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 Survival Follow-Up until death, withdrawal of consent, or the end of the study, whichever occurs first.

5.7 Treatment After Initial Evidence of Radiologic Disease Progression

Immunotherapeutic agents may produce antitumor effects by potentiating endogenous cancer-specific immune responses which may be functionally anergic. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents, and can manifest a clinical response after an initial increase in tumor burden or even the appearance of new lesions. In subjects who have initial evidence of radiological PD following a first course of treatment, it is at the discretion of the treating physician whether to continue a subject on study treatment for a second treatment course. This decision should be based on the clinical judgment of the subject's overall clinical condition, including performance status, clinical symptoms, laboratory data, and tolerance for study treatments.

Subjects recommended to receive a second treatment course after PD should meet the following criteria:

- Absence of signs and symptoms indicating disease progression
- Absence of progressive tumor at critical anatomical sites (e.g., cord compression) requiring urgent alternative medical intervention
- Absence of rapid progression of disease
- No decline in ECOG performance status

This allowance takes into account the observation that some subjects can have a transient tumor flare in the first few months after the start of immunotherapy, but with subsequent disease response.

5.8 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

6.1 Study Flow Chart

Trial Period:		**Treatment Courses[1]**													**Post-Treatment**	
Treatment Cycle/Title:	**Study Screening**	**1**			**2**			**3**			**4**			Safety Follow-Up	Surveill-ance Follow-Up[2]	Survival Follow-Up[3]
Treatment Week		1	2	3	4	5	6	7	8	9	10	11	12			
Scheduling Window (Days):	-28 to -1	±2	±2	±2	±2	±2	±2	±2			±2		±7	30 (±7) days post EOT[4]	Every 12 (±1) week post EOT	Every 12 (±1) week
Administrative Procedures																
Informed Consent																
Inclusion/Exclusion Criteria	X															
Demographics and Medical History	X															
Prior and Concomitant Medication Review	X															
Pembrolizumab Administration		X			X			X			X					
SQ IL-2 Administration		X[5]	X[5]	X[5]	X[5]	X[5]	X[5]									
IV IL-2 Administration		X[6]			X[6]											
Post-study anticancer therapy status														X	X	X
Survival Status														X	X	X
Clinical Procedures / Assessments																
Review Adverse Events		X	X[7,8]	X[7]	X	X[7,8]	X[7]	X			X			X		
Physical Examination	X	X	X[7,8]	X[7]	X	X[7,8]	X[7]	X			X			X	X	
Vital Signs[9] and Weight	X	X	X[7,8]	X[7]	X	X[7,8]	X[7]	X			X			X	X	
ECOG Performance Status	X	X	X[7,8]	X[7]	X	X[7,8]	X[7]	X			X			X	X	
Laboratory Procedures/Assessments: analysis performed by local laboratory																
Pregnancy Test – Urine or Serum β-HCG [10]	X	X[10]												X		

Trial Period:		**Treatment Courses[1]**												**Post-Treatment**	
Treatment Cycle/Title:	**Study Screening**	**1**			**2**			**3**			**4**			Safety Follow-Up	Surveill-ance Follow-Up[2]	Survival Follow-Up[3]
Treatment Week		1	2	3	4	5	6	7	8	9	10	11	12			
Scheduling Window (Days):	-28 to -1	±2	±2	±2	±2	±2	±2	±2			±2		±7	30 (±7) days post EOT[4]	Every 12 (±1) week post EOT	Every 12 (±1) week
HIV, Hepatitis-B and -C[11]	X															
PT/INR and aPTT	X[6]															
CBC with Differential	X	X[12]	X[7,8]	X[7]	X	X[7,8]	X[7]	X			X			X	X	
Basic Metabolic Panel	X	X[12]	X[7,8]	X[7]	X	X[7,8]	X[7]	X			X			X	X	
Hepatic Function Panel w/LD	X	X[12]	X[7,8]	X[7]	X	X[7,8]	X[7]	X			X			X	X	
FT4 and TSH	X	X[12]			X			X			X			X	X	
Amylase and Lipase	X	X[12]			X			X			X			X		
Troponin-I	X	X			X			X[13]			X[13]					
Urinalysis	X															
EKG	X															
Cardiac Function Testing[14]	X															
Pulmonary Function Testing[15]	X															
Cardiac Stress Testing[16]	X															
Efficacy Measurements																
Tumor Imaging[17]	X												X		X	
Achival Tissue Collection / Tumor Biopsy / Correlative Studies																
Archival or Newly Obtained Tissue Collection		X[18]														
Peripheral blood for T cell subset quantitation by flow cytometry		X[18]						X					X		X	

Trial Period:		**Treatment Courses[1]**												**Post-Treatment**	
Treatment Cycle/Title:	**Study Screening**	**1**			**2**			**3**			**4**			Safety Follow-Up	Surveill-ance Follow-Up[2]	Survival Follow-Up[3]
Treatment Week		1	2	3	4	5	6	7	8	9	10	11	12			
Scheduling Window (Days):	-28 to -1	±2	±2	±2	±2	±2	±2	±2			±2		±7	30 (±7) days post EOT[4]	Every 12 (±1) week post EOT	Every 12 (±1) week
Peripheral blood for future correlative studies		X[18]											X		X	

[1]Maximum duration of therapy is 3 courses.

[2]Post-treatment surveillance for patients with SD, PR, or CR.

[3]After PD, start of new cancer treatment, or completion of 1 year Surveillance Follow-Up

[4]EOT = end of treatment

[5]Dose Level 1 patients only. For each cycle day 1, administer IL-2 after pembrolizumab. Observe patients ≥ 1 hour after the first pembrolizumab dose (day 1, cycle1) before administering the first SQ IL-2 dose.

[6]Dose Level 2 and 3 patients only. Patients will admit to begin IV IL-2 treatment on cycle day 2, (or next available ICU admission day).

[7]Evaluations for Dose Level 1 patients week 2,3,5,6 are only required during Course 1

[8]Evaluations for Dose Level 2 and 3 patients on week 2 and 5 follow hospital discharge for IL-2 cycles 1 and 2 respectively.

[9]Vital signs to include temperature, heart rate, respiratory rate, blood pressure, and pulse oximetry.

[10]A negative pregnancy test must be documented < 72 hrs before each day 1 pembrolizumab dose for the start of each treatment course and at EOT. Pregnancy testing should be repeated whenever an expected menstrual cycle is missed or when pregnancy is otherwise suspected.

[11]Screening serologies within 28 days of day1

[12]Don't repeat labs cycle 1/day 1 if screening labs are < 14 days old.

[13]Troponin-I testing prior to pembrolizumab cycle 3 and 4 required for course 1 only

[14]LVEF ≥ 50% measured by MUGA scan, echo, or stress test study with myocardial perfusion imaging. A cardiac study documenting LVEF ≥ 50% (MUGA, echo, or stress testing) obtained prior to study enrollment and within 6 months of study day 1 is acceptable screening and does not need to be repeated.

[15]Screening studies for Dose Level 2 and 3 patients only. PFT testing completed prior to study enrollment and within 6 months of study day 1 is acceptable screening and does not need to be repeated

[16]Myocardial ischemia screening by normal/negative cardiac stress testing with myocardial perfusion imaging. **OR** cardiac catheterization with non-significant angiogram findings reviewed by a Cardiology consultant. Prior normal cardiac stress testing or negative cardiac angiogram findings obtained prior to study enrollment and within 6 months of study day 1 is acceptable screening and does not need to be repeated.

[17]Baseline imaging to include brain (MRI preferred; contrast CT acceptable) and chest, abdomen, and pelvis by CT or MRI. Bone scan required for patients with known bone involvement on CT or MRI. Restaging assessments to include chest, abdomen, pelvis body parts with brain imaging or bone scan required only for patients with tumor findings on

these studies at baseline. Body imaging studies obtained prior to study enrollment and ≤ 6 weeks from the start of study treatment are acceptable as baseline studies and do not need to be repeated.

[18]Collect blood samples for all eligible patients after screening is completed and before C1D1 treatment. Blood samples can be collected before C1D1 or on C1D1 before treatment is given. Confirmation of available archival tissue samples prior to C1D1 treatment.

7.0 TRIAL PROCEDURES

7.1 Subject Registration

All subjects will be registered and entered into the University of Washington protocol accrual and patient tracking system. Patients must be registered prior to starting protocol therapy.

Documented informed consent, HIPAA authorization, and verification of subject eligibility must be completed prior to subject registration and assignment of a unique study number.

If a patient is consented to the trial but is not registered or is withdrawn prior to initiation of protocol treatment, the reason for screen failure and/or withdrawal will be documented. However, no clinical trial data will be collected beyond the basic demographic data contained on the eligibility checklist. The site (University of Washington) will use a registration log with entries for each patient registered.

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 investigator and/or Merck for reasons related to subject safety.

7.2.1 Administrative Procedures

7.2.1.1 General Informed Consent

Consent must be documented by the subject's dated signature on a consent form along with the dated signature of the person conducting the consent discussion. The investigator will obtain documented consent from each potential subject prior to conducting any study procedures in the clinical trial.

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 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.

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 an 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

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

7.2.1.4.2 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 7.3.

7.2.1.5 Disease Details and Treatments

7.2.1.5.1 Disease Details

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

7.2.1.5.2 Prior Treatment Details

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

7.2.1.5.3 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.

7.2.2 Clinical Procedures/Assessments

7.2.2.1 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 the NCI CTCAE v5.0 (see Section 13.2). 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).

Please refer to section 7.3 for detailed information regarding the assessment and recording of AEs.

7.2.2.2 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 complete physical exam should also be performed at monitoring visits performed during the Treatment and Follow-Up phases of the study.

7.2.2.3 Vital Signs

Vital signs will be collected 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, blood pressure and pulse oximetry.

7.2.2.4 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG status (see Section 13.1) at screening, prior to the administration of each dose of trial treatment and discontinuation of trial treatment as specified in the Trial Flow Chart.

7.2.2.5 Tumor Imaging and Assessment of Disease

Tumor imaging by CT or MRI scans will be obtained at screening, at the end of each treatment course, and every 12 weeks following completion of therapy for patients who remain in Surveillance Follow-Up as specified in the Trial Flow Chart (Section 6.0). Disease status will be assessed versus baseline imaging for response category by RECIST 1.1 criteria (see Section 13.3).

7.2.2.6 Tumor Tissue Collection and Correlative Studies Blood Sampling

Blood and tissue collections for correlative studies will be obtained as specified in the Trial Flow Chart (Section 6.0).

7.2.3 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 6.

Table 6 Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
WBC (total and differential)	Lactate dehydrogenase (LDH)	Specific gravity	Serum β-human chorionic gonadotropin†
Hemoglobin	Amylase	pH	(β-hCG)†
Hematocrit	Lipase	Protein	
MCV	Aspartate aminotransferase (AST)	Glucose	PT (INR)
Platelet count	Alanine aminotransferase (ALT)	Ketones	aPTT
	Alkaline phosphatase	Bilirubin, Qual	Free tyroxine (T4)
	Total Bilirubin	Occult Blood	Thyroid stimulating hormone (TSH)
	Direct Bilirubin	Nitrite	Troponin-I
	Total protein	Leukocyte Esterase	
	Albumin	Urobilinogen	Blood for correlative studies
		Microscopic exam *(If abnormal)*	
	Sodium	results are noted	
	Potassium		
	Chloride	Urine pregnancy test †	
	Carbon Dioxide		
	Glucose		
	Blood Urea Nitrogen		
	Creatinine		
	Calcium		
† Perform on women of childbearing potential only. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required.			

Laboratory tests for screening or entry into the Second Course Phase should be performed within 14 days prior to the first dose of treatment. After pembrolizumab Cycle 1, pre-dose laboratory procedures can be conducted up to 72 hours prior to dosing. Results must be reviewed by the investigator or qualified designee and found to be acceptable prior to each dose of trial treatment.

7.2.4 Other Procedures

7.2.4.1 Discontinuation

When a subject discontinues study treatment 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 should be followed in accordance with the safety requirements outlined in Section 7.3 - Assessing and Recording Adverse Events. Subjects who attain a CR should return to the site for a Safety Follow-Up Visit (described in Section 7.2.5.2) and then proceed to the Surveillance Follow-Up Period of the study (described in Section 7.2.5.2.1).

7.2.5 Visit Requirements

Visit requirements are outlined in Section 6.0 - Trial Flow Chart. Specific procedure-related details are provided above in Section 7.2 - Trial Procedures.

7.2.5.1 Safety Follow-Up Visit

The mandatory Safety Follow-Up Visit should be conducted 30 (±7) days after the last dose of trial treatment or before the initiation of a new anti-cancer treatment, whichever comes first. All treatment-related 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 should also be followed and recorded.

7.2.5.2 Surveillance Follow-Up Visits

Subjects who complete or discontinue trial treatment with a disease status of CR, PR or SD will move into the Surveillance Follow-Up Phase and should be assessed every 12 weeks (84 ± 7 days) by radiologic imaging to monitor disease status. Every effort should be made to collect information regarding disease status until the start of new anti-neoplastic therapy, disease progression, death, or end of the study. Information regarding post-study anti-neoplastic treatment will be collected if new treatment is initiated.

7.2.5.2.1 Survival Follow-Up

Once a subject experiences confirmed disease progression or starts a new anti-cancer therapy, the subject moves into the Survival Follow-Up phase and should be contacted by telephone every 12 weeks to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first. Survival Follow ends for all patients when the last treated patient on study completes the Follow-Up Phase (end of study).

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, is also an adverse event.

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

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

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

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

All adverse events will be recorded from the time the consent form is signed through 30 days following cessation of treatment and at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in section 7.3.3.1.

Adverse events will not be collected for subjects during the pre-screening period (for determination of archival tissue status) as long as that subject has not undergone any protocol-specified procedure or intervention. If the subject requires a blood draw, fresh tumor biopsy etc., the subject is first required to provide consent to the main study and AEs will be captured according to guidelines for standard AE reporting.

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

For purposes of this trial, an overdose will be defined as any dose exceeding the prescribed dose for pembrolizumab by 20% over the prescribed dose. No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, pembrolizumab should be

discontinued and 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 Principal Investigator and within 2 working days 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 Principal Investigator 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 the Principal Investigator and to Merck

7.3.3.1 Serious Adverse Events

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

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

Refer to Table 7 for additional details regarding each of the above criteria.

Progression of the cancer under study is not considered an adverse event unless it results in hospitalization or death.

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 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 Principal Investigator and to Merck.

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

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

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

7.3.3.2 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 Principal Investigator 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 7.3.1 - 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.

1. Additional adverse events:

   A separate guidance document has been provided entitled "Event of Clinical Interest Guidance Document" (previously entitled, "Event of Clinical Interest and Immune-Related Adverse Event Guidance Document"). This document 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 or qualified designee will evaluate all adverse events according to the NCI Common Terminology for Adverse Events (CTCAE) v5.0. Any adverse event which changes CTCAE grade over the course of a given episode will have each change of grade recorded on the adverse event case report forms/worksheets.

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

Table 7 Evaluating Adverse Events

An investigator or qualified designee will evaluate all adverse events as to:

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

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

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.

8.0 DATA AND SAFETY MONITORING

8.1 Safety Requirements

At any time during the conduct of the trial, if it is the opinion of an investigator that the risks to the patient warrant early closure of the study, this recommendation should be made in writing to the Principal Investigator.

8.1.1 Accrual and Study Progress Oversight

The Principal Investigator will direct the formation of a Safety Data Review Board (SDRB) that will review study accrual and provide direction for dose escalations based on analysis of collected safety data including AE's, SAE's and DLT's. The SDRB will consist of the Principal Investigator, designated sub-investigators, and study administrative staff. Meetings will occur after completion of each dose-level cohort and on an as needed basis to address unanticipated adverse events. Meeting minutes will be documented. Any significant safety findings will be reported to Fred Hutch/University of Washington Cancer Consortium Institutional Review Board (IRB).

8.1.2 Data Monitoring

Institutional support of trial monitoring will be in accordance with the Fred Hutch/University of Washington Cancer Consortium Institutional Data and Safety Monitoring Plan (DSMP). Under the provisions of this plan, Fred Hutch Clinical Research Support coordinates data and compliance monitoring conducted by consultants, contract research organizations, or Fred Hutch employees unaffiliated with the conduct of the study. Independent monitoring visits occur at specified intervals determined by the assessed risk level of the study and the findings of previous visits per the institutional DSMP.

In addition, protocols are reviewed at least annually and as needed by the Consortium Data and Safety Monitoring Committee (DSMC), Fred Hutch Scientific Review Committee (SRC) and the Fred Hutch/University of Washington Cancer Consortium Institutional Review Board (IRB). The review committees evaluate accrual, adverse events, stopping rules, and adherence to the applicable data and safety monitoring plan for studies actively enrolling or treating patients. The IRB reviews the study progress and safety information to assess continued acceptability of the risk-benefit ratio for human subjects. Approval of committees as applicable is necessary to continue the study.

The trial will comply with the standard guidelines set forth by these regulatory committees and other institutional, state and federal guidelines.

8.1.3 Auditing

All trials conducted at UW/SCCA are subject to audit by the institution or any regulatory authority.

8.2 Records

Case Report Forms (CRFs) for individual patients will be provided by the Principal Investigator.

8.3 Source Documents

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

All data entered in CRF's that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records.

8.4 Direct Access to Source Data and Documents

The investigator and institution will permit study-related monitoring, audits, EC review and regulatory inspection, providing direct access to all related source data / documents. The study is monitored under the Cancer Consortium Data and Safety Monitoring Plan (DSMP) which details the full scope and extent of monitoring and provides for immediate action in the event of the discovery of major deviations. CRFs and all source documents, including progress notes and copies of laboratory and medical test results, must be available at all times for review by the clinical study monitor, auditor and inspection by health authorities (e.g. FDA).

9.0 STATISTICAL ANALYSIS PLAN

9.1 Statistical Analysis Plan

The primary objective of this study is to evaluate the safety of IL-2 in combination with pembrolizumab. Statistical analysis will be descriptive for observed toxicities.

The secondary objective is to evaluate clinical outcomes (CR, PR, ORR, DCR, PFS) in comparison to historical data among advanced RCC patients treated with HD IL-2 or anti-PD1 monotherapies. The target enrollment for a conditional expansion cohort will be exploratory in nature, and no predictive statistical analysis has been applied.

Progression-free survival will be defined from the time of registration to progression or death. Patients last known to be alive and progression-free will be censored at the date of their last disease assessment. PFS will be evaluated using the method of Kaplan-Meier. Median PFS times and associated 95% confidence interval will also be calculated.

Exploratory objectives include the evaluation of the PD-1 pathway. For this objective, PD-1 pathway protein expression measures will be correlated with clinical outcomes. Specifically, the

association between pre-treatment PD-L1 expression by IHC, TIL density and T cell subset identification for CD4+, CD8+ and Treg cells, and peripheral blood analysis to quantify lymphocyte subsets including CD4+/CD8+/Treg and overall response will be compared using logistic regression. In addition, the association between end of cycle peripheral blood re-analysis to quantify lymphocyte subsets including CD4+/CD8+/Treg and PFS will be evaluated using a Cox proportional hazards model, among patients alive and progression-free at end of treatment. Similarly, the association between PD-L1 expression by IHC and TIL density and T cell subset identification for CD4+, CD8+ effector and Treg cells at the end of treatment and PFS will be evaluated among patients who do not achieve a CR but are also progression-free and the end of treatment.

10.0 LABELING, PACKAGING, STORAGE AND DISPOSITION OF CLINICAL SUPPLIES

10.1 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 8.

Table 8 Product Description

Product Name & Potency	Dosage Form
pembrolizumab 100 mg/ 4mL	Solution for Injection

10.2 Packaging and Labeling Information

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

10.3 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.

10.4 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.

10.5 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.

11.0 STUDY TERMINATION

Discontinuation of individual study participant treatment may occur for reasons including patient decision to withdraw from study, unacceptable toxicity, disease progression, or investigator or Principal Investigator determination that it is not in the patient's best interest to remain on trial.

The study may be terminated prior to completion of planned enrollment and achievement of objectives if there is evidence that the study regimen is not tolerable.

The IRB will be notified about the completion or early termination of the trial.

12.0 ADMINISTRATIVE AND REGULATORY DETAILS

12.1 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.

13.0 APPENDICES

13.1 ECOG Performance Status

Table 9 ECOG Performance Status

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

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

13.2 Common Terminology Criteria for Adverse Events v5.0 (CTCAE)

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for adverse event reporting. (https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm)

13.3 Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 Criteria for Evaluating Response in Solid Tumors

RECIST version 1.1* will be used in this study for assessment of tumor response. While either CT or MRI may be utilized, as per RECIST 1.1, CT is the preferred imaging technique in this study.

* As published in the European Journal of Cancer:

E.A. Eisenhauer, P. Therasse, J. Bogaerts, L.H. Schwartz, D. Sargent, R. Ford, J. Dancey, S. Arbuck, S. Gwyther, M. Mooney, L. Rubinstein, L. Shankar, L. Dodd, R. Kaplan, D. Lacombe, J. Verweij. New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1). Eur J Cancer. 2009 Jan;45(2):228-47.

13.4 High-Dose Interleukin-2 (HDIL-2) Administration and Toxicity Management Guidelines

13.4.1 Overview

The toxicities of HDIL-2 result from a capillary leak syndrome that results in initial vasodilation/decreased systemic vascular resistance followed by leakage of fluid and albumin into interstitial spaces. The initial manifestations are hypotension and tachycardia that may develop as early as 2 hours after the first dose, often after an initial rigor and fever. Later manifestations include generalized body edema, total body rash, diarrhea, nausea, mild confusion and potentially acute renal failure.

13.4.2 Specific Toxicities and Corrective Intervention

13.4.2.1 Hemodynamics

- Hypotension
    - IV Fluids

      Upon admission for HDIL-2 treatment, patients should be started on maintenance intravenous fluids in anticipation of ensuing capillary leak syndrome, vasodilation and decreased systemic vascular resistance. Colloid has no advantage over crystalloid, even when the albumin falls, and D5LR at 100cc/hr is recommended. Bolus IV fluids and increase in the continuous IV rate may be of value for initial management of hypotension to keep MAP > 60, attempting to limit the cumulative positive fluid balance by the end of 5 days to no more than 10% of the patient's dry weight by the end of each 5-day cycle of HDIL-2. This is accomplished by the judicious balance of fluids and vasopressor agents, depending on the patient's hemodynamic status, renal function, acid-base balance and pulmonary reserve.

    - Vasopressor agents

      If hypotension persists despite judicious fluid resuscitation, vasopressor support with an α-sympathomimetic agent (generally phenylephrine) is indicated. Titration of phenylephrine should be between 0.5 and 2mcg/kg/min to keep the systolic blood pressure over 80-90 mm Hg (MAP > 60). Since the BP nadir tends to occur 4-6 hours after each dose of HDIL-2, a "reserve" should be available in the vasopressor dose, so that additional doses of HDIL-2 should be given only if the phenylephrine dose can be weaned to below about 1 mcg/kg/minute before the next IL-2 dose.

13.4.2.2 Renal

- Oliguria

Oliguria is universal and is due to the combination of hypotension/hypoperfusion and decreased intravascular volume. It may be amplified in uninephric patients and patients on vasopressors. Oliguria per se is not an indication for fluids or diuresis; a bladder scan or urinary catheter may be useful to better assess the renal status if the patient is anuric, acidotic or has other reasons for urinary retention.

13.4.2.3 Pulmonary

- Hypoxia

  The need for supplemental oxygen will vary among patients depending on their underlying lung function and disease. Supplemental oxygen should be used to keep the patient's oxygen saturation > 90-92%, and intravenous volume should be limited in patients whose oxygenation is difficult to maintain and in those with significant crackles and/or chest radiographic findings of pulmonary edema or significant pleural effusion.

- Cardiogenic Pulmonary Edema

  Cardiogenic pulmonary edema is extremely rare in patients receiving HDIL-2 since patients are well-screened and HDIL-2 rarely causes global cardiomyopathy. Any patient with sudden pulmonary decompensation should be evaluated for causes of cardiac origin.

13.4.2.4 Cardiac

- Ischemia

  Cardiac ischemia is also rare, but occasional focal myocarditis may occur, and arrhythmias or evidence of ischemia on EKG may mandate discontinuation of HDIL-2.

- Cardiac Arrhythmias

  Atrial cardiac arrhythmias during HDIL-2 treatment are uncommon, but occasionally supraventricular tachycardia and atrial fibrillation may be seen. Careful assessment should be performed for supervening causes such as ischemia, myocarditis, pericardial effusion or pulmonary events. Treatment should include antiarrhythmic medications, and does not preclude continuation of HDIL-2. Serious ventricular arrhythmias are rare and warrant discontinuation of HDIL-2 and resumption only if a minor, reversible/treatable cause was found.

- Edema

  Although patients often experience moderate amounts of peripheral edema at the end of each cycle, it is rare that they will experience severe symptoms from this extravascular fluid accumulation. Patients should be aggressively diuresed at the end of each cycle once they are hemodynamically stable.

13.4.3 Dosing

HDIL-2 is administered as cycles of a maximum of 14 doses given at 8-hour intervals. Doses that are skipped for management of toxicities are not compensated by lengthening the cycle. As a general rule, if a patient has severe enough toxicity to withhold 2 or more consecutive doses, IL-2 will probably need to be discontinued for the rest of that 5-day cycle.

Organ-by-organ guidelines for IL-2 dosing must be individualized and considered in the context of the whole patient rather than in isolation. Each dose should be given or withheld after an assessment of the patient by the RN and house officer, with consultation from the principal investigator or the SCCA HDIL-2 team, if needed.

Table 10 Organ-by-Organ Toxicity Guidelines for Holding IL-2 Dosing

System	Generally Safe to Give HDIL-2 (one or more present)	Consider Holding HDIL-2 Dose (Especially if >1-2 criteria present)	Unsafe to Give HDIL-2 (any criterion present)
Cardiac	Sinus tach up to 130 bpm, occasional ventricular ectopy	Sustained sinus tach after correction of contributing factor such as fever, chills, hypotension or significant ectopy	Ischemic ECG changes, atrial fibrillation, SVT, ongoing VT, elevated CPK/troponin
Dermatologic	Rash	Urticaria	Moist desquamation, bullae
Gastrointestinal	Mild diarrhea controlled with antimotility agents, isolated bilirubin elevation	Severe nausea, emesis, marked elevation/rise of transaminases	Ileus/abdominal distension, severe pain, intractable emesis
Hemodynamic	Phenylephrine support up to 1mcg/kg/min	Phenylephrine support up to 1.5mcg/kg/min – must be stable or titrating down before next dose	Phenylephrine support >1.5mcg/kg/min and or rising before next dose
Hemorrhagic/ Thrombotic	Thrombocytopenia	Clinically significant bleeding requiring platelet transfusions	Life threatening bleeding or clot
Infection	UTI, viral URI or localized HSV	Bacterial infection contributing to hemodynamic compromise	Infection requiring surgical intervention, or unresponsive to antibiotics
Metabolic	Asymptomatic and correctable: hypokalemia, hypocalcemia, hyperglycemia, hypophosphatemia, hypomagnesemia,	Symptomatic electrolyte or metabolic disturbance	Arrhythmia or other life threatening consequence or metabolic disturbance

Neurologic	Mild somnolence, vivid dreams	Mild confusion, hallucinations, patient aware	Moderate – severe confusion, hallucinations, patient unaware or combative, seizures
Pulmonary	Mild dyspnea, hypoxia responsive to 4L or less of oxygen	Moderate dyspnea, hypoxia requiring more than 40% oxygen, significant crackles, significant effusion not requiring treatment	Severe dyspnea, hypoxia on oxygen, intubation, severe pulmonary edema, effusions requiring thoracentesis
Renal	Creatinine up to 3, oliguria, correctable acidosis	Creatinine > 3, anuria or < 100cc/8 hours, persistent acidosis	Persistent anuria, dialysis for metabolic or renal indications

Additional management recommendations are based on published treatment guideline monographs by Schwartzentruber, et al. J. Immunother. (2001) 24:287 and by Dutcher, J. P. et al. JITC (2014) 2:26. [66, 67]

13.4.4 Supportive Medications Used During HDIL-2 Therapy

13.4.4.1 Standard supportive care

In order to minimize the toxicities of HDIL-2 treatment the following medications should be prescribed:

Table 11 Standard Supportive Medications

Medications	**Indications**
Acetaminophen 650 mg PO q4h	Fever, myalgias
NSAID (Example: Naproxen 500 or 750 mg PO BID)	Fever, myalgias
Proton pump inhibitor (Pantoprozole 40 mg PO/IV daily, or equivalent)	Gastritis
5HT3 blocker (Ex: Ondansetron 8 mg PO/IV daily, or prior to each dose of IL-2 as needed)	Nausea, emesis
Broad spectrum antibiotic, usually Levofloxacin 500 mg PO/IV daily	Infection

13.4.4.2 Symptom management

For management of toxicity related symptoms, the following should be prescribed on an as needed basis:

Table 12 As Needed Supportive Treatments

Medications	**Indications**
5HT3 blocker, as above, if not given prophylactically	Nausea
Benzodiazepine, usually Lorazepam 0.5 mg IV or 1 mg PO q4h	Mild nausea, anxiety
Butyrophenone, usually Haloperidol 1-5 mg IV q1h	Agitation, hallucination
Loperamide or Atropine-Diphenoxylate 1-2 tablets PO q4h, maximum 6 tablets/24h	Diarrhea
Meperidine 25 mg IV or morphine sulfate 1-2 mg, repeat up to twice at 10 minute intervals	Chills
Tucks topically	Perianal discomfort
Diphenhydramine 12.5-25 mg IV or 25-50 mg PO q4h	Pruritus
Hydroxyzine 10-25 mg PO q4h	Pruritus if paradoxical reaction to diphenhydramine
Aveeno bath, lotion	Severe pruritus
Lubriderm-based lotion	Pruritus, skin irritation
"Magic" mouthwash (Diphenhydramine/Aluminum hydroxide/Lidocaine)	Mouth irritation
Pseudoephedrine 30 mg PO q4h	Nasal congestion
Zolpidem or temazepam	Sleep
Phenylephrine 25 mg/250 mL concentration, Titrate to BPs 80-90, range 0.1-2 mcg/kg/min	Hypotension
Magnesium sulfate	Hypomagnesemia
Potassium or sodium phosphate	Hypophosphatemia
Potassium chloride	Hypokalemia

13.4.5 Additional Management Guidelines

Table 13 Additional Management Guidelines

Symptom/sign	**Intervention**
Anemia	Transfuse to keep Hct 27-30
Arrhythmia	Correct other factors, R/O ischemia,effusions; arrhythmia specific treatment; Consider resuming IL-2 on or off anti-arrhythmic treatment
Acidosis	Keep bicarb level >20
Edema, threatening compartment syndromes	Elevation, attention to neuropathic symptoms

Fever pattern atypical (late spike)	Culture, look for sources of bacterial infection
Hypoalbuminemia	No specific treatment
Hypocalcemia	Correct for low albumin, replace to normal values
Infection documented	Continuation of IL-2 depends on severity, interventions needed
Other electrolyte disturbances	Look for contributors, replace as needed

13.4.6 Monitoring

13.4.6.1 Monitoring guidelines: ICU routine

13.4.6.2 Labs:

- on admission (if not done on same day in clinic), CBC/plts/diff, PT/INR, chem. BMP/LFT/Mg/Phos,
- Daily CBC/plts/LFT/Mg/Phos
- Twice daily BMP
- At least every other day PT/INR

13.4.7 Patient Management Following Completion of HDIL-2

Since the hemodynamic effects of HDIL-2 begin to wane within hours of the last infusion, it is usually sufficient to wean the patient off pressors as rapidly as tolerated, followed by or accompanied by (depending on the patient's particular hemodynamic needs and volume status) prompt discontinuation of parenteral fluids and then active diuresis. Patients should have sufficient pulmonary reserve at the time of discharge to tolerate the possibility of mobilizing a few liters back into the vascular space (which can result in pulmonary edema) AND should be given at least 3-4 days of oral diuretics, with K as indicated, to return them to near dry weight (which is likely to be about 2-3 kg below their prior weight). Patients can stop the diuretics on their own when their weight normalizes and/or edema resolves. All patients experience desquamation and dry, pruritic skin, which is managed symptomatically with lubricants and anti-pruritics (avoiding steroid).

Patients should be discharged with their PICC line in place between cycles 1 and 2**.**

13.5. Contraceptive Guidance and Pregnancy Testing

13.5.1. Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below)

Women in the following categories are not considered WOCBP:

- Premenarchal
- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

  Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with two FSH measurements in the postmenopausal range is required.
  - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

13.5.2. Contraception Requirements

13.5.2.1. Male Participants:

Male participants with female partners of childbearing potential are eligible to participate if they agree to one of the following during the protocol defined time frame in section 5.5.2:

- Be abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent
- Use of a male condom plus partner use of a contraceptive method with a failure rate of <1% per year as described in Table 14 when having penile-vaginal intercourse with a woman of childbearing potential who is not currently pregnant.

  Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration.

13.5.2.2. Female Participants:

Female participants of childbearing potential are eligible to participate if they agree to one of the following during the protocol defined time frame in section 5.5.2:

- Be abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent
- Use a highly effective method of contraception consistently and correctly as described in Table 14 during the protocol-defined time frame in section 5.5.2 in combination with their male patterners use of a condom.

Table 14 Highly Effective Contraception Methods

Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of <1% per year when used consistently and correctly.*
● Combined (estrogen- and progestogen- containing) hormonal contraception [b] ○ Oral ○ Intravaginal ○ Transdermal ○ Injectable
● Progestogen-only hormonal contraception [b] ○ Oral ○ Injectable
Highly Effective Methods That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
● Progestogen- only contraceptive implant [b] ● Intrauterine hormone-releasing system (IUS) [b] ● Intrauterine device (IUD) ● Bilateral tubal occlusion
● **Vasectomized partner** A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
Notes: a) Typical use failure rates may be higher than perfect-use failure rates (i.e. when used consistently and correctly). b) Hormonal contraception efficacy is possibly decreased due to interaction with study treatments; therefore condoms must be used in addition to the hormonal contraception during the treatment period and follow up after the last dose of study treatment as specified in section 5.5.2.

Pregnancy Testing
WOCBP should only be included after a negative highly sensitive urine or serum pregnancy test.

Following initiation of treatment, pregnancy testing will be performed whenever an expected menstrual cycle is missed or when pregnancy is otherwise suspected; and at the time points specified in the Trial Flow Chart (Section 6.0).

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