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Phase II Trial of Avelumab (Bavencio®) with IL-15 in Subjects with Clear-Cell Renal Carcinoma

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Investigational Agents:

Drug Name:	Avelumab (MSB0010718C, Bavencio®, NSC #799232)	Recombinant human IL-15 (rhIL-15-NSC #745101)
IND Number:	100820	
Sponsor:	Center for Cancer Research, NCI	
Manufacturer:	EMD Serono, Inc. (Company Study/Tracking #: MS100070-0207)	Biopharmaceutical Development Program (BDP)/Leidos Biomedical Research, Inc. under contract with DCTD,NCI
Supplier:	EMD Serono, Inc.	Cancer Therapy Evaluation Program (CTEP), Division of Cancer Treatment and Diagnosis (DCTD), NCI

Commercial Agents: None

PRÉCIS

Background:

- Clear-cell renal cell carcinoma (ccRCC) is among the 10 most frequent diagnostic cancers in the United States with more than an estimated 62,000 new cases in 2016. The prognosis for patients with metastatic disease is poor with survival rates of 8%.
- The immunologic effects of recombinant human Interleukin-15 (rhIL-15), a stimulatory cytokine that promotes the differentiation and activation of NK cells, monocytes and long-term CD8+ memory T-cells, has been assessed in several Phase 1 trials in cancer patients.
- Avelumab is an anti-programmed death ligand-1 (PD-L1) fully human IgG1 antibody that inhibits PD1/PD-L1 interactions while leaving the PD1/PD-L2 pathway intact and enhances immune activation against tumor cells. It has received U.S. FDA accelerated approval for the treatment of patients with metastatic Merkel cell carcinoma (MCC) and urothelial carcinoma.
- Unlike other approved anti-PD-L1/PD1 antibodies, avelumab induces lysis of tumor cells via antibody-dependent cell-mediated cytotoxicity (ADCC), indicating an additional mechanism of action. However, avelumab has not shown ADCC against normal immune cell subsets in humans.
- More than 50% of ccRCC is PD-L1+ with higher expression in unfavorable prognostic tumors. Since the anti-PD-L1 antibody avelumab has shown ADCC activity *in vitro*, agents that may enhance ADCC by increasing number and activity of Fc-binding effector cells — such as rhIL15 — could improve efficacy of avelumab in this disease.

Objectives:

- Determine the efficacy of combined continuous intravenous infusion (CIV) rhIL-15 and avelumab treatment in patients with anti-PD-1/PD-L1 refractory metastatic clear cell renal carcinoma (ccRCC) by assessing the overall response rate

Eligibility:

- Age $\geq$ 18 years of age
- ECOG performance status of $\leq$ 1
- Histologically proven metastatic clear cell renal carcinoma with $\geq$ 5% expression of PD-L1 in the tumor area confirmed by IHC
- Patients must have failed or relapsed and have progressive disease after at least 2 prior therapies that include multityrosine kinase inhibitor like axitinib or sunitinib and an anti-PD1 or PD-L1 immune checkpoint inhibitor therapy like nivolumab which could have been administered in combination with an anti-CTLA4 agent like ipilimumab
- Adequate organ and marrow function

Design:

- Open-label, single-center, non-randomized Phase II study

- Safety Run-in Cohort with 3-6 patients at dose level 2mcg/kg and 4mcg/kg CIV IL-15 (recommended phase II dose) will ensure safety of recommended phase II dose rhIL-15 with fixed dose avelumab with Dose Expansion Cohort at 4mcg/kg dose level
- Efficacy of the combination will be assessed in a Simon two-stage phase II design with 9 or 17 patients depending on demonstration of clinical activity in the initial group of 9 patients
- Maximum 4 cycles (28-day cycle) of combination therapy
- To explore both Safety Run-in Cohort and further evaluation in a Dose Expansion Cohort, the accrual ceiling will be set at 25 patients

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STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; an IRB determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

1 INTRODUCTION

1.1 STUDY OBJECTIVES

1.1.1 Primary Objective

- Determine the efficacy of combined continuous intravenous infusion (CIV) rhIL-15 and avelumab treatment in patients with anti-PD-1/PD-L1 refractory metastatic clear cell renal carcinoma (ccRCC) by assessing the overall response rate.

1.1.2 Secondary Objectives

- Evaluate duration of response, progression-free survival and overall survival following combined CIV IL-15 and avelumab treatment
- Assess the safety and tolerability of combined CIV IL-15 and avelumab treatment
- Analyze the changes in peripheral blood lymphocyte subsets before and after treatment with rhIL-15 and avelumab
- Define the effects of rhIL-15 on the antibody-dependent cell-mediated cytotoxicity (ADCC) mediated by avelumab, using ex-vivo peripheral blood mononuclear cells (PBMCs)
- Examine treatment related changes in tumor deposits by immunohistochemical and molecular analysis of core biopsies obtained before and during treatment with rhIL-15 and avelumab

1.2 BACKGROUND AND RATIONALE

1.2.1 Disease Characteristics of Clear-cell Renal Carcinoma

Clear-cell renal cell carcinoma (ccRCC) is among the 10 most frequent diagnostic cancers in the United States with more than an estimated 62,000 new cases in 2016 [1, 2]. The prognosis for patients with metastatic disease is poor with survival rates of 8% [3, 4]. ccRCC is associated with mutations of VHL, an essential component of the cellular oxygen pathway. VHL, located on chromosome 3p, is inactivated by a mutation in 52% of ccRCC [5]. Several other genes show mutations at lower frequencies than VHLs. These genes include PBRM1 (40%), SETD2 (15%) and BAP1 (15%) which are all part of the chromatin remodeling histone methylation pathway [6]. Like VHL, these three genes are located within a 50-Mb region on the short arm of chromosome 3p.

1.2.2 Systemic Treatment of ccRCC

In the past 10 years treatment options for metastatic kidney cancer have expanded and improved substantially. Interferon alpha (IFNα) has been replaced by antiangiogenics, tyrosine kinase inhibitors, molecular therapeutics, new cytokines and recently immune checkpoint inhibitors (ICIs) with higher response rates (RRs), longer progression free survival and overall survival [7]. Other drugs used to treat ccRCC include antiangiogenic drugs, that target vascular endothelial growth factor (VEGF), VEGF receptors or platelet derived growth factor (PDGF) and include bevacizumab, axitinib, pazopanib, sorafenib, sunitinib, Cabozantinib and lenvatinib. The molecular target of rapamycin (mTOR) inhibitors utilized in the treatment of ccRCC are everolimus and temsirolimus [8-20]. High-dose IL-2 (HDIL-2) therapy, with a durable complete response rate (CR) of 9% and recognized partial response rate (PR) of 12%, remains a less commonly employed treatment largely due to the fact that this treatment is only appropriate for a

minority of very fit patients who are able to safely tolerate this intense regimen. Retrospective analysis of outcome for this treatment has more precisely defined the patient profile with higher likelihood of responding rates but has not identified strategies to expand the number of treatable patients or demonstrated more stringent patient selection has substantial impact on RR or survival in a prospective clinical trial [21-24]. Preclinical animal experiments identified Programmed cell death protein 1 (PD1) expression on CD8+ effector cells as a sign of exhaustion of the viral specific immune responses. The expression of Program death ligand (PD-L1) on tumor cells, sometimes on adjacent stroma cells or other leukocytes in the tumor milieu was also shown to deliver an immune dampening signal through PD-1 on effector lymphocytes. The combination of these 2 findings established the rationale for anti-PD1/PD-L1 treatment of metastatic cancers [25, 26]. Interestingly the preclinical animal data did not demonstrate the striking benefit that has subsequently been seen in the treatment of cancer patients [27, 28]. The initial reports of single agent clinical trials with nivolumab demonstrated response rates in the 20 to 35% range for metastatic melanoma or renal cell carcinoma and 15 to 20% range for patients with relapsed refractory non-small cell lung cancer (NSCLC) [27, 29, 30]. Subsequent publications have demonstrated clinical activity for pembrolizumab, atezolizumab, durvalumab and avelumab (Bavencio) and other anti-PD1/PD-L1 agents in patients with (transitional cell) bladder cancer, Hodgkin's lymphoma (HL), non-Hodgkin's follicular lymphoma (FL) and squamous cell head and neck cancer (SCCH&N) [31-33]. The combination of nivolumab plus ipilimumab, an anticytotoxic lymphocyte-associated protein 4 (CTLA-4) checkpoint inhibitor, has been shown to be more effective than nivolumab alone in several solid tumors including metastatic renal cell carcinoma (mRCC), albeit at the cost of significantly more toxicity [28].

1.2.3 Expression of PD-L1 in Renal Cell Carcinoma

There is a wide range of reported levels of PD-L1 positivity (PD-L1$^+$) depending on the particular PD-L1 antibody used in the immunohistochemical analysis, the histologic subtype of the RCC and whether assessment is scored only for the malignant cells or includes stromal and infiltrating immune effector cells. Conservative estimates for PD-L1 expression are usually based on data obtained from nephrectomy specimens most often reporting that 20% of mRCC are PD-L1+ [34]. Closer appraisal of PD-L1 expression in ccRCC revealed that PD-L1 positivity was associated with female gender, lymph node metastases, distant metastases, higher AJCC stage and advanced stage. Most importantly, the poorer prognostic tumors were more likely to express PD-L1 [35]. In a review of 177 patients more than half of the pathologically stage 3 or 4 (pT3/4) and more than 75% of the G2 tumors were PD-L1$^+$. In an analysis of 85 ccRCC patients who received high dose IL-2, 58% of tumors were PD-L1$^+$ [36]. Another retrospective analysis of 115 surgical specimens similarly 56.5% of the patients' tumors were PD-L1$^+$ [37]. A higher percentage of tumors from patients with sarcomatoid variant mRCC are reported to be PD-L1$^+$ [38].

1.2.4 Immune Checkpoint Inhibitor Treatment in Renal Cell Carcinoma

When the initial clinical data for MDX-1106, now nivolumab were first reported, it was clear that this agent had significant activity in mRCC [27]. Confirming what had been intimated in the first-in-human phase I trial for multiple tumor types, the subsequent report for 296 nivolumab patients showed a response rate (RRs) of 27% (9/33) in the cohort of renal cell patients [30]. The issue of the appropriate dose for nivolumab in the treatment of mRCC was largely settled in a randomized phase II trial that assessed 3 dose levels (0.3, 2 and 10 mg/kg) which demonstrated almost identical RRs of 20, 22 and 20% respectively for the 3 dose levels [39]. A subsequent comparative trial of nivolumab versus everolimus demonstrated a similar level of nivolumab activity with a RR of 25%

[40]. The Nivolumab Ipilimumab combination was tested in the CheckMate trials 016 and 214 and showed appreciable activity (40.4 and 42% RRs) albeit with a significantly higher rate of adverse events (AEs) [28]. As a result of these clinical trials, nivolumab either as monotherapy or in combination with ipilimumab for higher risk patients is now FDA approved for the treatment of mRCC.

Based on the generally positive results with anti-PD-L1/PD1 treatments including the nivolumab data, many commercial sponsors have developed agents targeting the PD-L1/PD1 axis that also have shown efficacy in mRCC. A phase I trial of atezolizumab in mRCC that included some patients with non-clear cell histology tumors showed an overall RR of 15% and a median progression free survival (PFS) of 5.6 months [41]. Most of the PD-1 and PD-L1 agents have now established effective fixed dosage schedules that eliminates the need for weight-based dose adjustments for individual patients and simplified treatment delivery [42]. There is additional clinical data for combination treatment with anti-PD-L1/PD1 agents and other biological response modifiers (BRMs)or targeted therapies that shows clinical activity in the treatment of mRCC. A phase I trial of pembrolizumab with the 4-1BB/CD137 agonist antibody PF-05082556) showed 1CR, 1 PR and 2 stable disease (SD) in 4 of the 5 mRCC patients treated in the trial [43]. The positive results from a phase 1b trial of Avelumab plus Axitinib [44] showed impressive activity in post nephrectomy treatment naïve mRCC with an overall response rate of 58% (32 of 55 patients) was validated by the recent results of the large (886 patients) randomized phase III Javelin 101 that compared this combination treatment to sunitinib in advanced previously untreated RCC patients and led to FDA approval of this combination as first line treatment for mRCC. The Avelumab plus Axitinib treatment produced a significantly better objective response rate (ORR) 51.4% versus 25.7% ($p< 0.001$) and progression free survival (PFS) 13.8 versus 8.4 months ($p=0.0001$) in all patients [45]. It is too early to analyze differences in overall survival for the 2 treatment arms. Treatment related AEs for patients receiving the Avelumab plus Axitinib combination in both trials were similar and substantial with 71% of the patients having $\geq$ grade 3 AE and discontinuation of treatment of study treatment in 22.8%, but the rate of these events were comparable to the Sunitinib patients (71.5% rate of $\geq$ grade 3 AEs and 13.4% discontinued treatment). Deaths due to treatment related toxicities in the phase III were almost identical (0.7% versus 0.2%). Additional clinical trials examining combination regimens with Nivolumab, Pembrolizumab, Atezolizumab, Durvalumab and Avelumab in multiple malignancies are currently ongoing [46, 47].

1.2.5 Avelumab (Bavencio)

When overexpressed in tumors, PD-L1 is a negative prognostic marker due to T-cell anergy induced by the binding of PD-L1 to PD1 [31, 33]. Avelumab (Bavencio) is a fully human IgG1 antibody directed against programmed death ligand-1 (PD-L1) protein. Avelumab inhibits PD1/PD-L1 interactions while leaving the PD1/PD-L2 pathway intact, enhances immune activation against tumor cells and has been evaluated in the treatment of multiple refractory solid tumor patients [31-33, 48-51]. Avelumab (Bavencio) has received accelerated approval in the United States from the FDA for the treatment of patients with metastatic Merkel cell carcinoma (MCC) [52] and urothelial carcinoma [49]. Unlike other approved anti-PD-L1/PD1 antibodies, avelumab has an additional potential mechanism of action that induces lysis of tumor cells *in vitro* via antibody-dependent cell-mediated cytotoxicity (ADCC) that has yet to be confirmed *in vivo* in patients with normal immune T-cell subsets [53] but has been demonstrated by in vitro testing [54]. The standard avelumab treatment regimen is 10 mcg/kg given every 2 weeks. The drug is

well tolerated by patients and has a toxicity spectrum similar to other anti-PD-1 or PD-L1 treatments summarized below in **Table 1** and **Table 2** with most notable AEs being fatigue, infusion reactions, followed by skin changes and GI toxicity [54-56].

1.2.6 Adverse Events in Avelumab Clinical Trials

The safety experience in phase I Javelin Solid Tumor protocol (1650 patients) and phase 2 Javelin Merkel 200 clinical trial (88 patients) was recently updated [57]. The most common treatment related adverse events (TRAEs) of any grade were fatigue in 307 patients (17.7%) and infusion related reactions (IRR) in 295 patients (17.0%). **Table 1** from this report shown below lists the most common clinical and laboratory TRAEs. These therapy related events led to permanent discontinuation of treatment in 107 patients (6.2%). The most common cause of treatment discontinuation was immune related events (IRR) seen in 32 patients (1.8%), gamma-glutamyl transferase increase seen in 7 patients (0.4%), increased alanine aminotransferase in 4 patients 0.2%), increased creatine phosphokinase (CPK) in 4 patients (0.2%), and fatigue in 4 patients (0.2%). One hundred and eight patients (6.2%) had serious TRAEs again most commonly immune related (15 patients; 0.9%), pneumonitis (11 patients; 0.6%), pyrexia (6 patients; 0.3%), and adrenal insufficiency (5 patients; 0.3%). **Table 2** below lists the Immune Related Adverse Events (irAE assessed by the CTC version 4.0 grading criteria) which were seen in a small number of patients and generally were grade 3 AEs

Table 1: Avelumab Most Common TRAEs

Most Common Adverse Treatment Related Events N= 1738		
TRAE	**Any Grade No (%)**	**> Grade 3 No (%)**
Any TRAE	1164 (67.0)	177 (10.2)
Fatigue	307 (17.7)	17 (1.0)
IRR[b]	295 (17.0)	10 (0.6)
Nausea	150 (8.6)	2 (0.1)
Diarrhea	123 (7.1)	5 (0.3)
Chills	116 (6.7)	0
Pyrexia	106 (6.1)	0
Decreased appetite	90 (5.2)	3 (0.2)
Hypothyroidism	87 (5.0)	3 (0.2)
AST increased	38 (2.2)	8 (0.5)
Lipase increased	25 (1.4)	17 (1.0)
GGT increased	17 (1.0)	10 (0.6)

Table 2: Immune-Related Adverse Events

Immune Related Adverse Events (irAEs)				
irAE[a]	**N = 1738 No. (%)**			
	Any Grade	**Grade 3**	**Grade 4**	**Grade 5**
Any irAE	247 (14.2)	32 (1.8)	4 (0.2)	3 (0.2)
Rash	90 (5.2)	1 (0.1)	0	0

Immune Related Adverse Events (irAEs)				
Colitis	26 (1.5)	7 (0.4)	0	0
Pneumonitis	21 (1.2)	5 (0.3)	1 (0.1)	1 (0.1)
Hepatitis	16 (0.9)	11 (0.6)	0	2 (0.1)
Endocrinopathies	106 (6.1)	6 (0.3)	0	0
Thyroid disorders	98 (5.6)	3 (0.2)	0	0
Adrenal insufficiency	8 (0.5)	1 (0.1)	0	0
Type 1 diabetes mellitus	2 (0.1)	2 (0.1)	0	0
All other irAEs	19 (1.1)	5 (0.3)	3 (0.2)	0
Blood CPK increased	5 (0.3)	1 (0.1)	2 (0.1)	0
Myositis	5 (0.3)	1 (0.1)	1 (0.1)	0
Psoriasis	5 (0.3)	1 (0.1)	0	0
Guillain-Barre syndrome	1 (0.1)	1 (0.1)	0	0
Systemic inflammatory response syndrome	1 (0.1)	1 (0.1)	0	0

1.2.7 Immune related risks

In addition, some clinically relevant irAEs were reported after the data cutoff or outside of the

Pooled Safety Dataset. These included: 3 events of nonfatal graft versus host disease (2 in the liver and 1 in skin) and 1 event of immune thrombocytopenic purpura in Study B9991007 (avelumab in subjects with cHL), 4 events of myasthenia gravis/myasthenic syndrome in the clinical studies, and overall 15 events of pancreatitis including one case of fatal pancreatitis necrotising in Study B9991003 with the combination of avelumab with axitinib in subjects with RCC (Investigator Brochure, 29May 2020).

1.2.8 Efficacy in Avelumab Clinical Trials

1.2.8.1 Metastatic Urothelial Cancer

The activity of avelumab in refractory metastatic urothelial carcinoma was assessed in 66 patients as part of the phase 1 Javelin trial [49]. An independent central assessment confirmed an overall response rate (ORR) of 18.2% including 5 patients (11.4%) with a complete response as seen in **Figure 1**. Three patients (6.8%) had a partial response and 15 patients with stable disease as best response. Patients' responses were predominantly those with PD-L1 positive tumors with seven of eight responding patients (87.5%) having PD-L1 positive tumors compared to only 1 of 24 (4.7%) patients with PD-L1 negative tumors having a response.

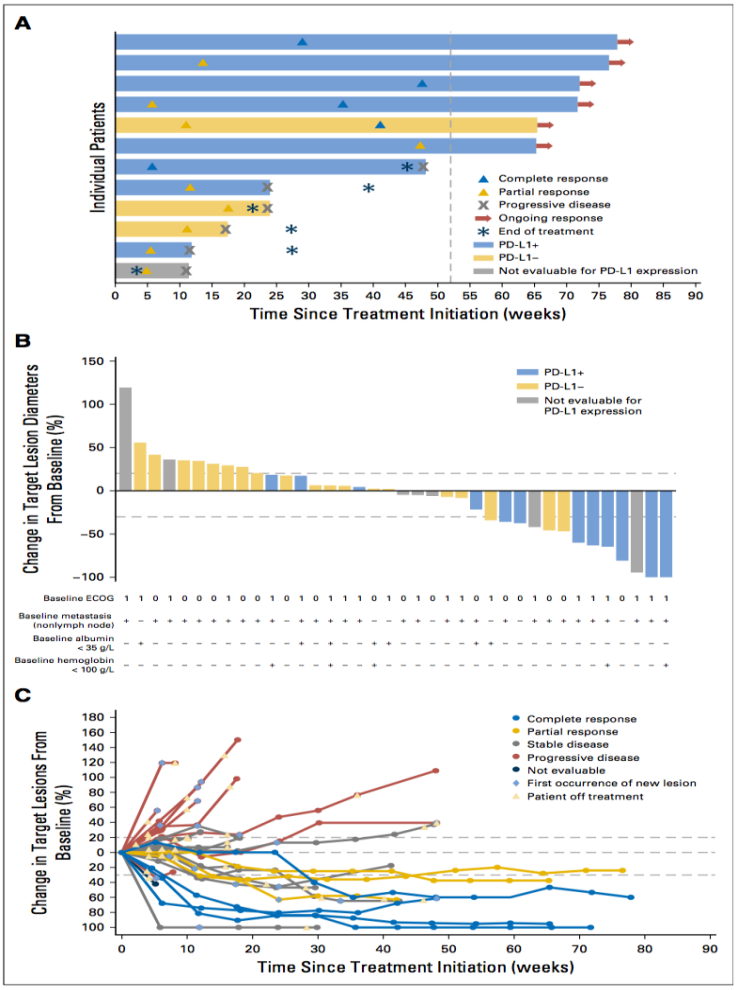

A
Individual Patients
Complete response
Partial response
Progressive disease
Ongoing response
End of treatment
PD-L1+
PD-L1−
Not evaluable for PD-L1 expression
Time Since Treatment Initiation (weeks)
B
Change in Target Lesion Diameters From Baseline (%)
PD-L1+
PD-L1−
Not evaluable for PD-L1 expression
Baseline ECOG
Baseline metastasis (nonlymph node)
Baseline albumin < 35 g/L
Baseline hemoglobin < 100 g/L
C
Change in Target Lesions From Baseline (%)
Complete response
Partial response
Stable disease
Progressive disease
Not evaluable
First occurrence of new lesion
Patient off treatment
Time Since Treatment Initiation (weeks)

Figure 1: Clinical activity of avelumab [49]:
(A) Time to response, duration of treatment, and duration of response to avelumab (eight confirmed responses and four unconfirmed responses as of data cutoff), with programmed death-ligand 1 (PD-L1) expression status indicated (on the basis of a ≥ 5% staining threshold on tumor cells; nonevaluable specimens [n = 7] included those that were missing, of poor quality, or otherwise not available to provide results). The vertical dotted line represents 1 year from the initiation of treatment. (B) Plot of tumor regression from baseline as measured by Response Evaluation Criteria in Solid Tumors (RECIST) in all assessable patients (n = 38), with PD-L1 expression status indicated (on the basis of a ≥ 5% staining threshold on tumor cells). Eastern Cooperative Oncology Group (ECOG) performance status, presence of non-lymph node metastasis, and albumin and hemoglobin levels at baseline are shown for each patient. The upper dotted line represents progression at 20% and the lower dotted line represents the RECIST boundary for complete response or partial response at 30%. (C) Percentage change in sum of target lesion diameters from baseline over time for all assessable patients (n = 38), defined as those patients with baseline tumor assessments and at least one postbaseline assessment. The upper dotted line represents progression at 20% and the lower dotted line represents the RECIST boundary for complete response or partial response at 30%

In addition to the tumor regressions, Avelumab had an impact on median progression free survival (mPFS) and median overall survival (mOS) in this patient population as seen below in **Figure 2**.

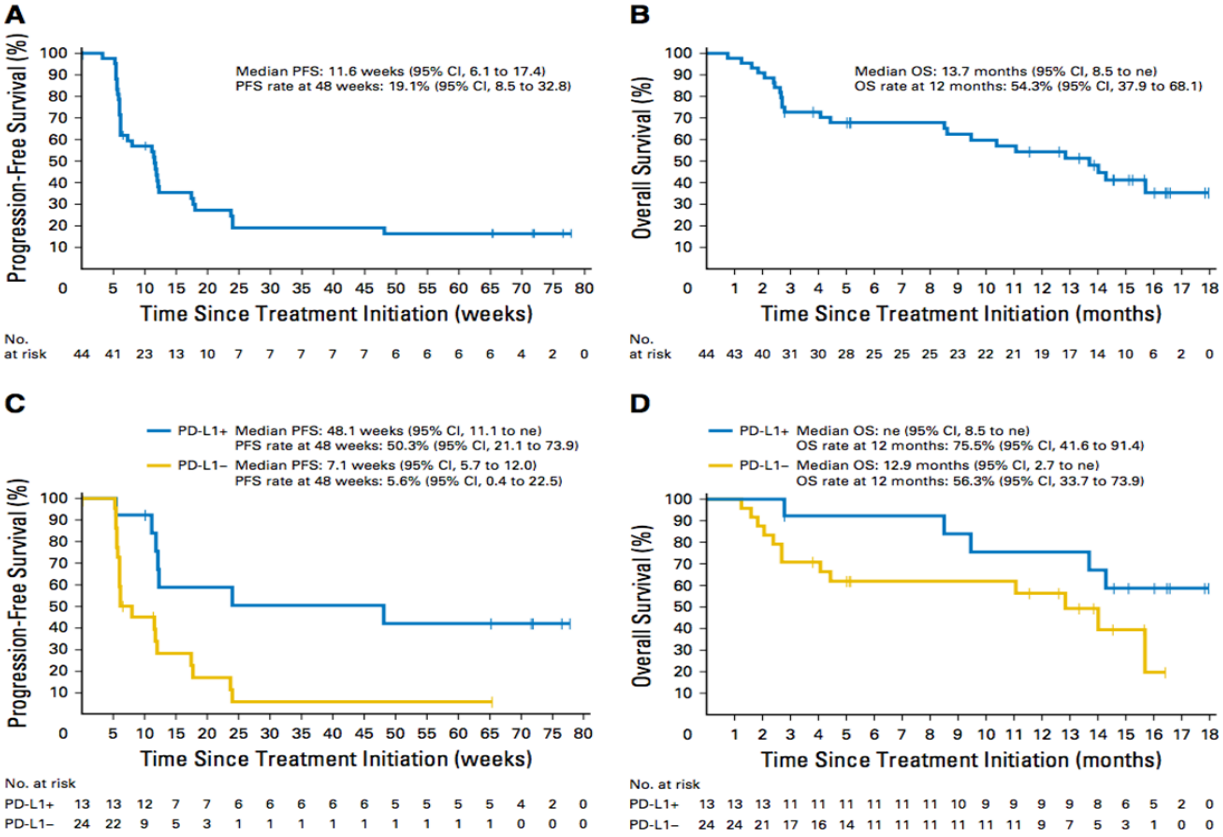


Figure 2: Progression-free survival (PFS) and overall survival (OS) [49]:
Kaplan-Meier estimate of PFS (A) and OS (B) for the overall study population (N = 44). Kaplan-Meier estimate of PFS (C) and OS (D) on the basis of programmed death-ligand 1 (PD-L1) expression on tumor cells (n = 37). Vertical lines show censored events. Positive PD-L1 expression was defined as >5% of tumor cells expressing PD-L1 at any intensity. ne, not estimable

1.2.8.2 Ovarian Cancer

A preliminary report has demonstrated clinical activity in patients with epithelial ovarian cancer [55] Additional ovarian cancer patients were subsequently treated and produced data for 124 relapsed ovarian cancer patients treated with avelumab. The response rate for this disease cohort is 9.7% (12 patients), all partial responses with 6 ongoing. Stable disease was observed in 44% of these patients that resulted in a disease control rate of 54% (unpublished data).

1.2.8.3 Non-small Cell Lung Cancer

In a phase Ib trial of 184 patients, objective responses were seen in 22 (12%) patients that were 1 CR, 21 PRs and 70 patients had stable disease (38%)[56] and resulted in a disease control rate (DCR) of 50%. The most common treatment-related AEs of any grade were fatigue (25%), infusion reactions (21%), and nausea (13%). Grade 3 or worse treatment-related AEs occurred in 13% of patients, with the two most common being infusion reactions (2%) and increased lipase level (2%).

1.2.8.4 Breast Cancer

Avelumab was studied in 168 patients with locally advanced or metastatic breast cancer refractory to or progressing after standard of care including 58 patients with triple negative breast cancer (TNBC) [58]. Response rate in the entire cohort was 3.0% and 5.2% in TNBC. Stable disease was observed in an additional 42 patients (25.0%) resulting in a DCR of 28.0%. Again, responses were predominantly in PD-L1 expressing tumors (unpublished data).

1.2.8.5 Merkel Cell Carcinoma

Merkel cell carcinoma (MCC) is a rare aggressive neuroendocrine tumor of the skin. The initial report of avelumab treatment of 88 MCC patients showed an objective response of 31.8% including 8 CRs and 20 PRs [52].

1.2.8.6 Renal Cell Carcinoma

There is preliminary evidence of clinical activity for avelumab in the treatment mRCC [59] as additional trials of avelumab for mesothelioma, gastric cancer, adrenocortical carcinoma and renal cancer are ongoing. Additionally, preclinical data from combination treatment with the chimeric anti-PD-L1/anti-TGFβ fusion molecule M7824 and IL-15 [53] demonstrated significantly augmented ADCC with human effector cells in vitro that support this combination treatment strategy.

1.2.8.7 Gastric Adenocarcinoma

Adenocarcinoma of the stomach and the closely related gastroesophageal junction (GEJ) are aggressive tumors that are rarely curable and require new and effective treatment options. The results of the phase 1 trial JAVELIN Solid Tumor JPN and the dose expansion cohort of metastatic gastric or GEJ adenocarcinoma was recently published [60].

1.2.9 Recombinant Human Interleukin-15 (rhIL-15)

IL-15 is a 14-15kDA member of the 4-alpha-helix bundle family of cytokines that acts through a heterotrimeric receptor involving IL-12/IL-15R beta (β)subunit shared with IL-2, the common gamma chain (γc) shared with IL-2, IL-4, IL-9, IL-21, and IL-15 specific receptor subunit IL-15R alpha (IL-15Rα) or CD215 [61] . IL-15 acts as a cell-surface molecule as part of an immunological synapse with IL-15 and IL-15R alpha produced in trans on adjacent mononuclear cells like monocytes and DCs which have been stimulated with interferon and/or CD40 ligation [62-65]. IL-

15 has been shown in many model systems to be a potent stimulator of T and NK-cell functions and in contrast to IL-2 does not activate Tregs and produces less capillary leak syndrome [61-63, 65, 66]. Multiple murine preclinical studies have demonstrated the efficacy of IL-15 in the treatment of cancer that led to clinical development of this cytokine. An intravenous bolus (IVB) regimen of IL-15 was evaluated in a rhesus macaque's toxicology experiment that administered 20 mcg/kg/day of IL-15 for 12 days and produced a 4 to 8-fold increase in the number of circulating NK cells [67, 68]. Administration of the same dose by continuous intravenous infusion (CIV) for 10 days produced a 10-fold increase in the number of circulating NK cells, a 15-fold increase in circulating monocytes and a massive 80 to 100-fold increase in circulating effector memory CD8 T-cells [69].When this same dose was given as a subcutaneous (SC) injection for 10 days, a 10-fold expansion in circulating effector memory CD8 T-cells and modest increases in NK cells was observed [69]. Based on animal and laboratory trials of IL-15, great interest was generated among leading immunotherapeutic experts participating in the NCI Immunotherapy Agent Workshop who ranked IL-15 as the most promising unavailable immunotherapeutic agent to be brought to therapeutic trials.

1.2.10 Clinical Experience with Single Agent rhIL-15 in the Treatment of Cancer

1.2.10.1 First in Human Intravenous Bolus (IVB) trial

The first in-human (FIH) phase I trial of rhIL-15 administered the treatment as rapid (30 minute) IV bolus (IVB) to adults with refractory metastatic malignant melanoma and metastatic renal cell cancer [70].-This study was initially planned with a starting dose of 3 mcg/kg/day given for 12 consecutive days. However, after the first patient treated developed grade 3 hypotension and after patient #5 at this dose level developed grade 3 thrombocytopenia, the protocol was amended to add the two lower doses of 1.0 and 0.3 mcg/kg/day with the expectation of returning to higher dose levels later. When two of four patients treated at the 1.0 mcg/kg/day dose unexpectantly developed asymptomatic grade 3 alanine aminotransferase (ALT) and aspartate aminotransferase (AST) elevations that were dose limiting, all subsequent patients were treated at the 0.3 mcg/kg dose level. All 9 patients with IL-15 at 0.3 mcg/kg/day received 12 doses without a DLT, and the maximum tolerated dose (MTD) of rhIL-15 was defined as 0.3 mcg/kg/day.

There was a consistent temporal pattern of post-treatment adverse events in patients receiving 3 mcg/kg/day doses of IL-15 with fever and rigors beginning 2 ½ to 4 hours following the start of IV infusions, soon after drops in blood pressure were seen with nadirs approximately 20 mm/Hg below pretreatment levels that responded slowly to rapid normal saline (NS) infusions. These physiologic changes were concurrent with an up to 50-fold elevation of serum IL-6 and interferon gamma (IFNγ) levels. Flow cytometry of peripheral blood lymphocytes in patients receiving 3 mcg/kg/day revealed a dramatic efflux of NK and memory CD8 T-cells from the circulation within minutes of IL-15 administration, gradual rise in NK cell numbers in the first 4 to 5 days of treatment, followed by an influx and hyperproliferation yielding a 10-fold expansion in the number of NK cells at the end of or after completion of the treatment cycle. A modest increase in the number of $CD8^+$ T-cells was also seen but virtually all of these $CD8^+$ T-cells were activated and expressed high levels of Ki67, CD38 and HLA-DR. In this first-in-human phase I trial there were no clinical responses with stable disease as the best response. However, 5 patients had decreases of between 10% and 30% of their marker lesions that included 2 patients that cleared their lung lesions.

1.2.10.2 Subsequent Clinical Trials with Subcutaneous (SC) or Continuous Intravenous (CIV) rhIL-15

The clinical toxicities that limited dose escalation in the IVB trial were associated with intense cytokine production within the first few hours of treatment and marked by exceedingly high IL-15 levels. Serum IL-15 concentrations at these levels would be sufficient to signal through the intermediate affinity (IL-2) IL-15Rβ and gamma chain (γc) receptor pair that resulted in the undesirable toxicities seen in the FIH trial and suggested that dosing strategies that limited the C_{max}, increased the duration of lower IL-15 levels that were optimal for high-affinity IL-15 αβγ receptor would improve the IL-15 stimulatory signal [71]. Alternative SC and CIV dosing regimens were evaluated first in non-human primate (NHP) rhesus macaques and subsequently in phase I clinical trials. The preclinical NHP experiments assessed the pharmacokinetics (PK) for multiple dose levels including the 20 mcg/kg dose given as an IVB (C_{max} 720 pg/mL) and produced more advantageous IL-15 concentration; C_{max} of 50 pg/mL for SC injections and C_{max} of 4 pg/mL for CIV infusion with more balanced PK parameters that stimulated greater expansion of NK and $CD8^+$ effector cells [67-69].

A phase I dose escalation trial (Clinical Trials Identifier: NCT01727076) performed in adults with refractory metastatic solid tumors that assessed a SC rhIL-15 treatment regimen (Monday-Friday for 2 consecutive weeks of a 4-week cycle) was performed under the direction of Cancer Immunotherapy Trials Network (CITN) at dose levels of 0.25, 0.5, 1, 2 and 3 mcg/kg/day[71]. Nineteen patients were treated with 14 patients receiving ≥ 2 cycles of treatment. Patients experienced common cytokine side effects of fevers, chills, fatigue, mild anorexia, transient biochemical laboratory abnormalities and transient lymphopenia. The MTD was 2 mcg/kg/day; with notable serious adverse events of pancreatitis at the 2.0 mcg/kg dose level and grade 3 cardiac chest pain at the 3mcg/kg dose level. Flow-cytometry data demonstrated > 10-fold increase in NK cells, an approximately 3-fold increase in CD8 cells at the 2 highest dose levels and a dramatic increase in the frequency of $CD56^{bright}$ CD3 ^{negative} NK cells that peaked about 3 days after the last injection on day 15 of the treatment cycle. Again, stable disease was the best response, but 1 patient remained on treatment for 2 years without progression but relapsed soon after the rhIL-15 was stopped. This protocol defined a safe immunostimulatory regimen that could be given as an outpatient in future combination treatment protocols [71].

A parallel phase I dose escalation trial (Clinical Trials Identifier NCT01572493) was performed in adults with refractory metastatic cancers the Clinical Center NIH, rhIL-15 was administered to patients with metastatic malignancy by CIV for 10 days at progressively increasing doses to 3 patients each of 0.25, 0.5, 1.0, 2.0 and 4.0 mcg/kg/day. Two dose-limiting toxicities were observed at 4.0 mcg/kg/day, one hepatotoxicity and the other visceral arterial ischemia making 2 mcg/kg the MTD that was well tolerated in the 9 patients treated at this dose [72]. The PK data from the CIV regimen was notably different from the IVB regimen having an appreciably lower C_{max} 5662 pg/mL (2 mcg/kg cohort) compared to 30,420 pg/mL (for 3 mcg/kg cohort). The serum IL-15 level was largely maintained in the CIVrhIL-15 treated patients over the first 48 hours compared to the rapid decline seen in the IVB patients with serum half-life of approximately 2 ½ hours. Patients in the CIV trial showed a much lower serum IL-15 level during the last 2 to 3 days of the infusion that was approximately 10% of their C_{max} level. which is believed to be related to the high number of high affinity IL-15 receptor bearing effector cells acting as a sink rapidly binding and clearing the free serum IL-15. More limited PK data from the SC treatment protocol showed fairly comparable C_{max} 6480 pg/mL (for 3 mcg/kg cohort) 4 hours after injection that is largely gone by

24 hours post injection. As predicted in the NHP toxicology studies the lower but sustained IL-15 levels produced by the SC and CIV regimens produced the large increase in activated effector cells at the higher dose levels in the respective trials

The CIV regimen produced characteristic changes in lymphocyte numbers with early lymphopenia (days 1 to 3) for both T and NK cells, followed by a gradual increase in cell numbers and dramatic rise in cells (30 to 80-fold increase in NK cells, 2 to 6-fold increase in $CD8^{+}$ cells and 350-fold increase in $CD56^{bright}$ NK cells) during the 48 hours after completion of the treatment as shown below in Figure 3[(77)]. The rate of proliferation of different subsets of NK cells assessed by Ki67 was consistent with their levels of CD122 (IL-2/IL-15Rβ) expression with $CD56^{bright}$ > $CD56^{dim}$, $CD94^{high}$, > $CD56^{dim}$, $CD94^{low}$. The functional capacity of the dominant $CD56^{bright}$ subset was augmented following IL-15 administration and was associated with an increase in their expression of perforin and granzyme. Although the specific lytic activity of $CD56^{bright}$ cells was not as great as that of $CD56^{dim}$ cells, their single cell lytic and antibody-dependent cellular cytotoxicity (ADCC) activity were markedly increased by rhIL-15 treatment. This ADCC activity was confirmed in assays with anti-CD20 antibody coated Raji cells, natural cytotoxicity to K562 cells, mediated by NKp30 and NKp46 as well as by MICA/NKG2D-mediated cytotoxicity [73]. These clinical trial results and preclinical data combining ICI, anti-CTLA4 and anti-PD1, with rhIL-15 [74, 75]and antitumor antibodies promote the development of clinical trials with these combinations [76].

The CIVrhIL-15 trial was subsequently amended to evaluate a 5-day (120 hour) regimen with further dose escalation at 3, 4 and 5 mcg/kg/day. Ten additional patients have been safely treated at these dose levels without DLTs or remarkable toxicities. Common adverse events (AEs) as expected have been the fatigue, fevers, chills or occasional rigors, capillary leak syndrome and reversible laboratory abnormalities. As seen in table 2, this 5-day regimen has produced impressive increases in absolute lymphocyte count (maximum ALC 25,000 to 30,000 cells/mL, NK cells (30 to > 80-fold increase) and CD8 cells (5 to 8-fold increase) that generally has been higher than seen in the patients treated at the 2 mcg/kg dose level for 10 days.

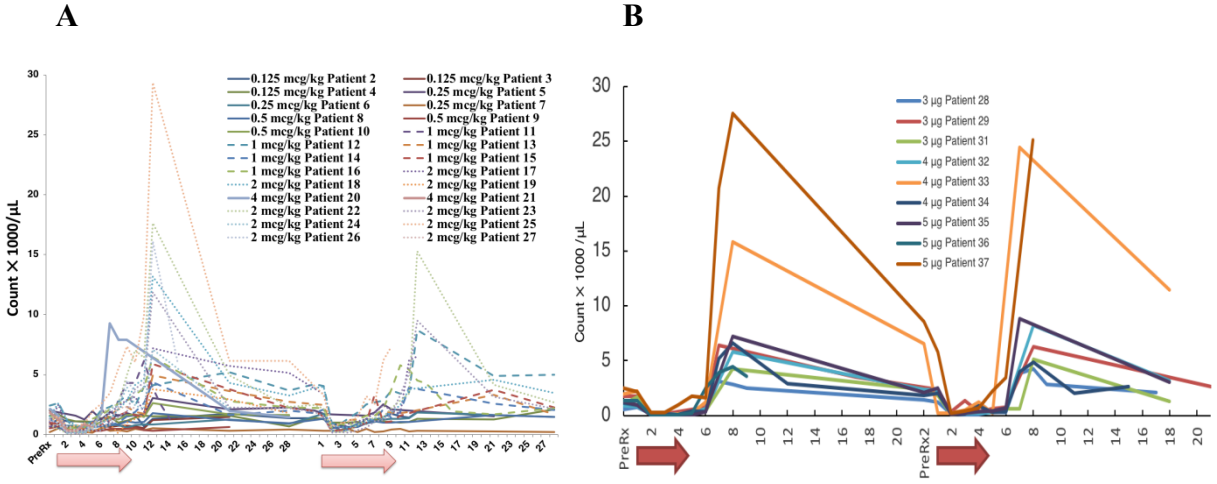


Figure 3: Increase in lymphocytes, predominantly NK cell count, during continuous infusion of rhIL-15. rhIL-15 was administered at progressively increasing doses of 0.25, 0.5, 1.0, 2.0 and 4.0 mcg/kg/day by 10-day civ infusion (A) and 5-day civ infusion (B) to patients with metastatic malignancy. Patients 2-4 received 0.125 mcg/kg, patients 5-7 received 0.25 mcg/kg, patients 8-10 received 0.5 mcg/kg, patients 11-16

received 1.0 mcg/kg and patients 17-19 received 2.0 mcg/kg. Following termination of the treatment (red arrow) there was a dramatic 30-fold increase in the number of circulating lymphocytes predominantly NK cell count and an over 350-fold increase in the number of circulating CD56bright NK cells in the 10-day cohort, and an up to 44-fold increase (33-fold mean increase) in the number of circulating NK cells in the 5-day cohort.

Table 3: Characteristics and Outcomes of 11 patients treated with a 5-day civ rhIL-15 infusion

Diagnosis	Age	Gender	Dose level (mcg/kg)	No. of doses	NK cell increase (fold)	CD8+ T-cell increase (fold)
Melanoma	63	M	5	5	32.01	4.21
Small bowel	69	M	5	10	39.13	4.74
Colorectal	60	F	5	4	-	-
Small bowel	51	F	5	10	32.03	5.66
Colorectal	66	F	4	10	44.90	3.65
Renal cell	56	M	4	15	43.65	8.94
Esophageal	60	M	4	10	39.63	2.01
Colorectal	67	F	3	20	21.40	1.65
Colorectal	56	F	3	15	23.66	2.03
Endometrial	70	F	3	3	-	-
Colorectal	47	F	3	10	24.15	1.66

The complete absence of anti-IL-15 antibodies seen in patients treated with IV E. coli rhIL-15 which contrasts with the experience in patients receiving any formulation of rhIL-15 as a SC injection is justification for the increased patient effort required to receive CIV rather than SC rhIL-15 treatment. The clinical experience is that all SC rhIL-15 treatment regimens have been reported to generate neutralizing anti-IL-15 antibodies that are associated with a decrement in immune activation after continuing multicycle treatment [71-78].

1.3 Considerations and Rationale for Phase II Design

The safety database for the rhIL-15 being used in this trial has data from more than 80 patients, mostly monotherapy IV patients, but recently patients have been treated with rhIL-15 in combination with antitumor monoclonal antibodies and checkpoint inhibitors [76, 78]. The side effects of rhIL-15 have been all closely linked to the patients' period of treatment without any episodes of delayed toxicity which commonly resolve soon after IV treatment is discontinued and therefore are distinct from the expected toxicities of avelumab. With the CIVrhIL-15 regimen, fevers, fatigue, myalgias, chills with occasional rigors, dry skin with infrequent rashes are the most common symptomatic side effects. Capillary leak characterized by decreased serum albumin and fluid input exceeding urinary output, modest decrease in blood pressure and possibly some pulmonary capillary leak seen in the 4 or 5 mcg/kg dosing cohorts evidenced by slight drops in oxygen saturation have been observed in the previously treated CIV rhIL-15 patients. Common

laboratory abnormalities include early (treatment days 1-4) leukopenia, lymphopenia, thrombocytopenia, transaminitis, anemia, hypoalbuminemia during the whole treatment cycle, late cycle rises in bilirubin in patients treated with doses ≥ 2 mcg/kg and the dramatic spike in lymphocytes that occurs in the 72 hours after completion of the CIV infusion. The norm is for most of these laboratory abnormalities to begin returning or to resolve to baseline while treatment continues. There has been no evidence of increased risk of infection or requirement for antibiotic treatment during the period of cytopenias or increased bleeding during the period of decreased platelets. Decreases in hemoglobin (Hgb), which most likely is related to increased sequestration of red blood cells in the liver and spleen, generally require more time to return to pretreatment levels. This incidence of anemia has possibly been greater in the patients treated with the 5-day regimen and the 3, 4 or 5 mcg/kg dose levels, but this assessment has been complicated by the fact that 8 of the 10 patients treated in these dosing cohorts have GI malignancies and were found to be iron deficient. Some patients were transfused during their 2nd or later cycle of treatment and those who tolerated oral iron replacement therapy had replenishment of their iron stores to improve their Hgb level. A number of the patients previously treated in the rhIL-15 trials had past history of autoimmune phenomena related to their prior cancer treatment with checkpoint inhibitors and none of these patients developed new or recurrent autoimmune toxicities.

As seen in **Figure 4**, the rate and severity of irAEs is also generally lower for anti-PD-L1 agents [77], including avelumab (**Table 4**), with the onset of the clinical events of greatest concern occurring generally 2 to 3 months after initiation of treatment. Avelumab has been approved by the FDA for the treatment of metastatic refractory urothelial cancers, has a safety database that exceeds 2000 patients and has a very well characterized AE profile [57].

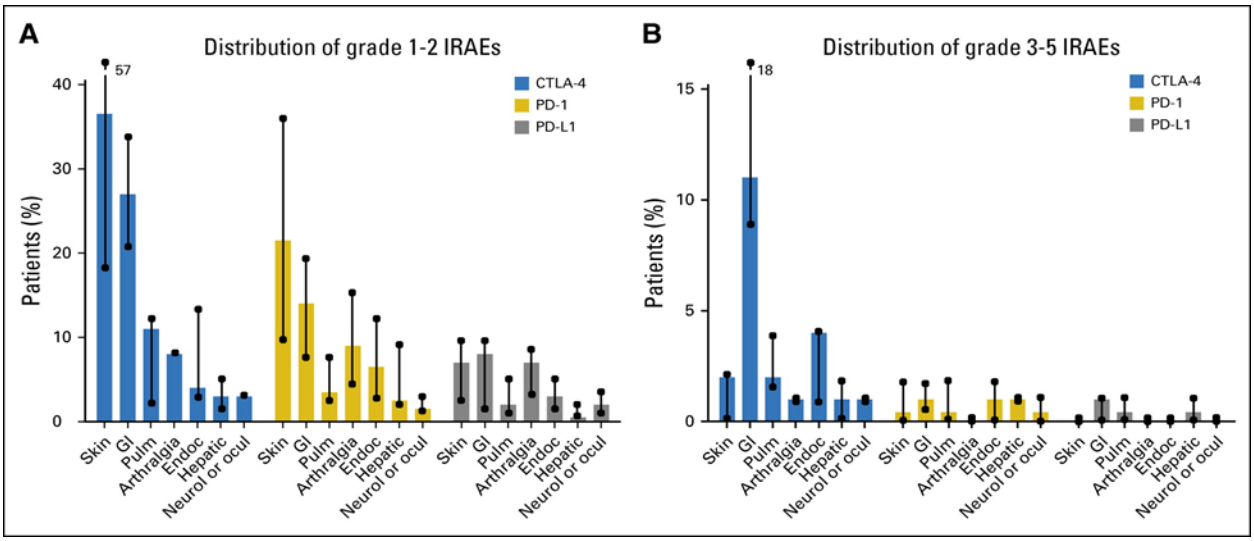


Figure 4: Distribution of irAEs for anti-PD-L1agents [77]
Distribution of (A) grade 1 to 2 and (B) grade 3 to 5 immune-related adverse events (irAEs) for all tumor types in the main clinical trials with anti– cytotoxic T-cell lymphocyte-4 (anti–CTLA-4), anti–programmed death 1 (PD-1), or anti–PD ligand 1 (PD-L1) antibodies as single therapies. The values quoted are the median (range) irAE rates for the set of clinical trials as a whole.

Table 4: Summary of irAEs in Avelumab Safety Database

irAE	Overall rate %	Grade 3 through 5%	Onset of Symptoms	
			Median	Range
Pneumonitis	1.2	0.5	2.5 months	3 days – 11 months
Hepatitis	0.9	0.5 (grade 3 only)	3.2 months	7 days -15 months
Colitis	1.5	0.4 (grade 3 only)	2.1 months	2 days – 11 months
Adrenal	0.5	0.1 (grade 3 only)	2.5 months	1 day – 8 months
Thyroid	6	0.2 (grade 3 only)	2.8 months	14 days – 13 months
Diabetes	0.1	0.1 (grade 3 only)	NA	NA
Nephritis	0.1	NA	NA	NA

Infusion reaction initially occurred in one quarter of the patients receiving avelumab including 9 patients with grade 3 (0.5%) and 3 patients with grade 4 (0.2%) events that were successfully controlled with antihistamines and IV corticosteroids. The avelumab package insert now recommends routine premedication with an antihistamine during the first 4 infusions. Anti-PD-1 (nivolumab, pembrolizumab or PDR001) antibodies have been given in combination with all versions of rhIL-15, E. coli (NCI produced) single chain agent, heterodimeric IL-15 (Novartis) and the ALT-803 superagonist (Altor now NantKWest). While the number of patients treated with these combinations is still modest, there has not been a new safety signal or evidence of synergistic toxicities. Given the close temporal relationship of CIV rhIL-15 treatment to the transient grade 3 hematologic and occasional metabolic abnormalities, we anticipate that these events will not complicate the recognition of the rare autoimmune events seen with avelumab which would normally become apparent during the second or third cycle of treatment. We believe it is reasonable to use our standard DLT exclusion algorithm even in the initial dose level safety evaluation of patients and will view sustained or delayed grade 3 elevations of liver function tests (LFTs) as DLTs.

2 ELIGIBILITY ASSESSMENT AND ENROLLMENT

2.1 ELIGIBILITY CRITERIA

2.1.1 Inclusion Criteria

2.1.1.1 Patients must have histologically proven metastatic clear cell renal carcinoma with ≥ 5% expression of PD-L1 in the tumor area confirmed by IHC in the NCI Lab of Pathology or performed by an outside CLIA certified laboratory using the FDA licensed Dako 28-8 or

22C3 antibodies PharmDx [79, 80]. Archival tumor sample may be used but if archival tissue is not available or is not adequate, tissue biopsy will be required.

2.1.1.2 Patients must have failed or relapsed and have progressive disease after at least 2 prior therapies that include multityrosine kinase inhibitor (mTKI) like axitinib or sunitinib and an anti-PD1 or PD-L1 (ICI) therapy like nivolumab which could have been administered in combination with an anti-CTLA4 agent like ipilimumab. Patients who received an ICI in combination with a mTKI would be eligible for the trial if they received another appropriate treatment. Adjuvant or neoadjuvant with either type of agent would not fulfill this requirement only treatment for metastatic disease will be considered to satisfy this criterion.

2.1.1.3 Disease must be measurable with at least one measurable lesion by RECIST v1.1 criteria (see Section **6.3**) that is different from the lesion biopsied.

2.1.1.4 Age ≥18 years

NOTE: Because no dosing or adverse event data are currently available on the use of rhIL-15 in combination with avelumab in patients <18 years of age, children are excluded from this study, but may be eligible for future pediatric trials

2.1.1.5 ECOG performance status ≤1 (Karnofsky ≥80%, see **APPENDIX A**)

2.1.1.6 Adequate organ and marrow function as defined below:

absolute neutrophil count	≥1,500/mcL
absolute lymphocyte count	≥500/mcL
Hemoglobin	≥10 g/dL
Platelets	≥100,000/mcL
total bilirubin	≤1.5 X institutional upper limit of normal (ULN)
AST(SGOT)/ALT(SGPT)	≤2.5 X institutional ULN
Serum creatinine	≤ 1.5 X institutional ULN
OR	
Creatinine clearance	≥50 mL/min/1.73 m^2 for patients with creatinine levels >1.5 institutional ULN

2.1.1.7 Negative serum or urine pregnancy test at screening for women of childbearing potential (WOCBP).

NOTE: WOCBP is defined as any female who has experienced menarche and who has not undergone successful surgical sterilization or who is not postmenopausal. WOCBP must have a negative pregnancy test (HCG blood or urine) during screening.

2.1.1.8 Women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry, for the duration of study participation, and 1 month after completion of rhIL-15 and avelumab administration. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately.

2.1.1.9 Ability of subject to understand and the willingness to sign a written informed consent

document.

2.1.2 Exclusion Criteria

2.1.2.1 Chemotherapy within 4 weeks (6 weeks for nitrosoureas or mitomycin C).

2.1.2.2 Persisting toxicity related to prior therapy of grade > 1, with the exception of the following: alopecia, sensory neuropathy grade ≤ 2, or other grade ≤ 2 not constituting a safety risk based on investigator's judgement.

2.1.2.3 Patients who are receiving any other investigational agents

2.1.2.4 Current use of immunosuppressive medication, EXCEPT for the following:

- Intranasal, inhaled, topical steroids, or local steroid injection (e.g., intra-articular injection)
- Systemic corticosteroids at physiologic doses ≤ 10 mg/day of prednisone or equivalent; or,
- Steroids as premedication for hypersensitivity reactions (e.g., CT scan premedication).

2.1.2.5 Patients with known brain metastases should be excluded from this clinical trial because of their poor prognosis and because they often develop progressive neurologic dysfunction that would confound the evaluation of neurologic and other adverse events.

2.1.2.6 Patients with previous malignant disease other than the target malignancy within the last 5 years with the exception of basal or squamous cell carcinoma of the skin or cervical carcinoma in situ.

2.1.2.7 Patients with history of any organ transplantation,

2.1.2.8 Vaccination within 4 weeks of the first dose of avelumab. Vaccination with a live vaccine while on trial is prohibited. **NOTE:** Seasonal influenza vaccines for injection are generally inactivated flu vaccines and are allowed; however intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines, and are not allowed.

2.1.2.9 Patients with history of allergic reactions attributed to compounds of similar chemical or biologic composition to rhIL-15 or avelumab.

2.1.2.10 Patients with uncontrolled intercurrent illness including, but not limited to, ongoing or active infection requiring systemic therapy, or psychiatric illness/social situations that would limit compliance with study requirements.

2.1.2.11 Inability or refusal to practice effective contraception during therapy or the presence of pregnancy or active breastfeeding. Based on its mechanism of action, avelumab can cause fetal harm when administered to a pregnant woman. Animal studies have demonstrated that inhibition of the PD-1/PD-L1 pathway can lead to increased risk of immune-mediated rejection of the developing fetus resulting in fetal death. These potential risks may also apply to other agents used in this study.

2.1.2.12 Patients with active bacterial infections, documented HIV infection or positive screening serology, PCR evidence for active or chronic hepatitis B or hepatitis C, or positive screening HBV/HCV serology without documentation of successful curative treatment (see Section **12.1** for IL-15 administration in HIV positive patients).

2.1.2.13 Patients with active or history of any autoimmune disease, including asthma requiring chronic inhaled or oral corticosteroids, or with history of asthma requiring mechanical ventilation; patients with a history of mild asthma that are on or can be switched to non-corticosteroid bronchodilator regimens are eligible

2.1.2.14 Cardiovascular disease: Clinically significant (i.e., active) cardiovascular disease: cerebral vascular accident/stroke (< 6 months prior to enrollment), myocardial infarction (< 6 months prior to enrollment), unstable angina, congestive heart failure (≥ New York Heart Association Classification Class II), or serious cardiac arrhythmia requiring medication

2.1.2.15 Other severe acute or chronic medical conditions including immune colitis, inflammatory bowel disease, immune pneumonitis, pulmonary fibrosis or psychiatric conditions including recent (within the past year) or active suicidal ideation or behavior; or laboratory abnormalities that may increase the risk associated with study participation or study treatment administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for entry into this study.

2.2 STRATEGIES FOR RECRUITMENT AND RETENTION

Study participants will be recruited from the population of patients screened in the lymphoid malignancies clinic of the National Institutes of Health. These will include both referrals from outside physicians as well as patient self-referrals. This study will be posted on NIH websites and on NIH social media forums. In addition, information will be provided on the ccr.cancer.gov/Lymphoid-Malignancies-Branch and ClinicalTrials.gov web pages, and on the official Lymphoid Malignancy Branch social media accounts.

2.3 SCREENING EVALUATION

2.3.1 Screening activities performed prior to obtaining informed consent

Minimal risk activities that may be performed before the subject has signed a consent include the following:

- Email, written, in person or telephone communications with prospective subjects
- Review of existing medical records to include H&P, laboratory studies, etc.
- Review of existing MRI, x-ray, or CT images
- Review of existing photographs or videos
- Review of existing pathology specimens/reports from a specimen obtained for diagnostic purposes.

2.3.2 Screening activities performed after a consent for screening has been signed

The following activities will be performed only after the subject has signed the consent for study #01-C-0129 on which screening activities will be performed. Assessments performed at outside facilities or on another NIH protocol within the timeframes below may also be used to determine eligibility once a patient has signed consent.

The following tests/procedures should be performed to determine treatment eligibility. Assessments and procedures to confirm study eligibility should be completed within 28 days prior to registration (unless otherwise noted). See also the Study Calendar provided in **APPENDIX F.**

2.3.3 Clinical Evaluations

- Disease history, including: diagnosis, treatment (e.g., systemic treatments, radiation and surgeries), status, and significant prior/ongoing side effects and symptoms
- Complete medical history including: all active conditions considered to be clinically significant by the treating investigator
- Physical examination, including: height (screening only), weight, vital signs (i.e., temperature, pulse, respiratory rate, oxygen saturation and blood pressure); review of concomitant medications and symptoms/side effects; and, assessment of performance status

2.3.4 Laboratory Evaluations

NOTE: Results from outside NIH are accepted.

- Hematological Profile: CBC with differential and reticulocyte count
- Biochemical Profile: Creatinine (i.e., Acute Care Panel); serum calcium, phosphate, magnesium and albumin (i.e., Mineral Panel); ALT, AST, total and direct (if required) bilirubin (i.e., Hepatic Panel); 24-hour urine creatinine clearance (if needed to measure CrCl in cases where serum creatinine >1.5mg/dl); and LDH
- Serum Lipase and Amylase
- Coagulation panel, including: PT/INR and a PTT
- Thyroid function tests, including: thyroid stimulating hormone (TSH) and free thyroxine (T4)

- HIV, and hepatitis: Hepatitis B surface antigen (HBsAg), Hepatitis B core antibody, Hepatitis C antibody (HCV) [qualitative], HIV 1/2 antibody (qualitative) **NOTE:** For individuals with a positive hepatitis B core antibody, HBV DNA PCR will be performed to screen for subclinical infection. For individuals with a positive hepatitis C antibody, HCV RNA RT-PCR will be performed to determine infectious status.
- Serum or urine pregnancy test (B-HCG) in women of childbearing potential
- Urinalysis (with microscopic examination if abnormal)
- Antinuclear antibody (ANA), rheumatoid factor (RF) and anti-thyroid antibody
- Creatine phosphokinase (CPK), troponin
- Flow cytometry and lymphocyte sets, and subsets

2.3.5 Imaging Studies

NOTE: Results from outside NIH are accepted. Other body areas may be imaged if clinically indicated.

- CT, chest, abdomen, pelvis and neck (if required). CT should be performed with IV and PO contrast, unless patient is allergic or has renal insufficiency; other imaging may be substituted at the discretion of the investigator [such as MRI].
- PET/CT torso (extremities to be included if there is confirmed or suspected disease involvement) maybe performed in selected cases to better evaluate lesions of uncertain etiology
- Patients with neurological symptoms or signs should undergo MRI scan of the brain and lumbar puncture.

2.3.6 Other Procedures

- Pathological review/confirmation of diagnosis by Laboratory of Pathology, NCI (no time limit) and PD-L1 staining as outlined in Section **5.2.4.1**. If no prior samples are available, punch or core biopsy of an appropriate easily accessible tumor deposit will be performed.
- Patients with significant pulmonary or smoking history, including significant pulmonary involvement by tumor, pleural effusion, history of chronic obstructive pulmonary disease (COPD) or lobar or greater surgical resection of lung will require qualifying pulmonary function tests (PFTs) that include adjusted diffusing capacity (DLCO/Adj), forced expiratory volume in 1 second (FEV1).
- Cardiac Evaluation: Electrocardiogram (EKG), and for patients with significant history of vascular disease or clinical suspicion of cardiac dysfunction, a transthoracic echocardiogram will be obtained to ensure adequate cardiac performance to receive the protocol treatment without increased risk.

2.4 PARTICIPANT REGISTRATION AND STATUS UPDATE PROCEDURES

Registration and status updates (e.g. when a participant is taken off protocol therapy and when a participant is taken off-study) will take place per CCR SOP ADCR-2, CCR Participant Registration & Status Updates found here.

2.4.1 Treatment Assignment Procedures

NOTE: For NCI CCR registration purposes only

2.4.1.1 Cohorts

Number	Name	Description
1	Safety Run-in	Patients with relapsed/refractory PD-L1-expressing metastatic ccRCC who have progressive disease after at least 2 prior therapies that include multityrosine kinase inhibitor and an anti-PD1/PD-L1 inhibitor to determine safety of dose
2	Dose Expansion	Patients with relapsed/refractory PD-L1-expressing metastatic ccRCC who have progressive disease after at least 2 prior therapies that include multityrosine kinase inhibitor and an anti-PD1/PD-L1 inhibitor to determine efficacy of combination treatment

2.4.1.2 Arms

Number	Name	Description
1	Safety Run-in	IL-15 by CIV infusion at escalating doses of 2, and 4 mcg/kg/day on days 1-5 of each 28-day cycle (max 4 cycles) with avelumab by IV infusion at a dose of 800mg on Day 8 and 22 of each cycle, to determine safety of dose (3-6 patients per dose level)
2	Dose Expansion	IL-15 by CIV infusion at 4 mcg/kg/day on days 1-5 of cycles 1-4 with avelumab at 800mg on Day 8 and 22 of each cycle (Total 17 patients) to determine efficacy of treatment

2.4.1.3 Treatment Assignment

Treatment assignment is open-label, and non-randomized/non-stratified. Subjects in Cohort 1 are directly assigned to Arm 1. Subjects in Cohort 2 are directly assigned to Arm 2.

2.5 BASELINE EVALUATION

The following should be performed within 28 days prior to the first dose of rhIL-15 unless otherwise noted; test performed as part of screening do not need to be repeated if they were performed within the specified window prior to initiating treatment.

2.5.1 Clinical Evaluations

- Medical history (interim)
- Physical examination including weight, vital signs (i.e., temperature, pulse, respiratory rate, oxygen saturation and blood pressure); review of concomitant medications and symptoms/side effects; and assessment of performance status (ECOG performance score see **APPENDIX A**).

2.5.2 Laboratory Evaluations

NOTE: Results from outside NIH are accepted

- Required within 7 days:
  - Serum or urine pregnancy test (B-HCG) for women of childbearing potential
- Required within 14 days:
  - Hematological Profile: CBC with differential and reticulocyte count

- Biochemical Profile: Chemistry panels including: Acute Care (sodium, potassium, chloride, CO_2, glucose, BUN, creatinine), Mineral Panel (serum calcium, phosphate, magnesium and albumin), Hepatic Panel (alkaline phosphatase, ALT, AST, total and direct bilirubin), and 24-hour urine creatinine clearance (if needed measure CrCl if serum creatinine >1.5mg/dl)
- Others: LDH, troponin
- Serum Lipase and Amylase
- Thyroid panel: TSH and free T4
- Coagulation panel, including: PT/INR and aPTT
- Urinalysis (with microscopic examination if abnormal)
- IL-2R alpha

- Required within 28 days:
  - Antinuclear antibody (ANA), rheumatoid factor (RF) and anti-thyroid antibody

2.5.3 Imaging Studies

Every participant should have an evaluation of known sites of disease as part of baseline evaluation. **NOTE:** Results from outside the NIH are accepted if the films provide high quality images that can be used to measure tumor marker lesions.

- One or more of the following studies: CT, MRI, FDG-PET
- Patients with neurological symptoms or signs should undergo MRI scan* of the brain

*NOTE: The MRIs to be done in this study may involve the use of the contrast agent gadolinium, if clinically indicated. The risks associated with MRIs and contrast are discussed in the consent form.

2.5.4 Research Correlates

NOTE: See Section **5** for additional information. The following sample types will be collected for correlative research studies:

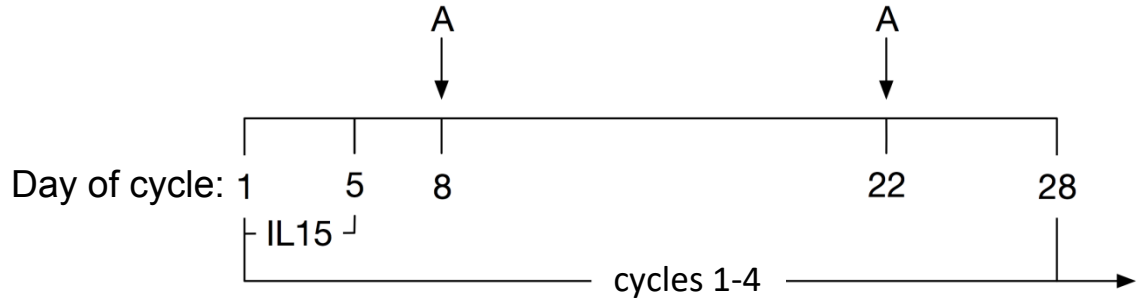
- Required:
  - Blood samples for lymphocyte subset testing and circulating tumor DNA
  - Tumor Tissue (archival or fresh) to assess PD-L1 expression for eligibility
  - Blood samples for ADCC of avelumab, tissue immune cell subset comparison (as outlined in Section **5**)
- Optional:
  - Pretreatment tumor biopsy to assess immune response to therapy can use the archival tissue or the fresh sample obtained to assess PD-L1 expression for protocol entry. Tissue sample for the optional on treatment biopsy obtained between cycle 1 day 22 and cycle 2 day 4 will be a core biopsy of easily accessible tumor deposits.

3 STUDY IMPLEMENTATION

3.1 STUDY DESIGN

In this Phase II trial of combination rhIL-15 and avelumab in patients with relapsed or refractory metastatic PD-L1+ ccRCC, IL-15 will be administered by CIV. The trial will begin with a small safety run-in cohort with a rhIL-15 starting dose of 2 mcg/kg/day, and a second dose level of 4 mcg/kg/day (the desired Phase II dose). There is clinical experience for the combination of anti-PD1 plus IL-15, but there is no prior safety experience for the combination of avelumab and E. coli derived rhIL-15. Consequently, the first 3 patients will begin CIV rhIL-15 treatment at a dose of 2 mcg/kg/day on days 1-5 and avelumab (800mg, by IV) on day 8 and 22 of the 28-day cycle (i.e., every 2 weeks). If one of these patients has a dose limiting toxicity (DLTs), three additional patients will be treated to establish the safety of the combination. Assuming there are no DLTs, subsequent patients will be treated at the 4 mcg/kg/day dose level. Again, the safety of this dose of rhIL-15 in combination will be established in a 3 to 6 patient cohort to confirm this treatment regimen does not pose unacceptable risk to the enrolled subjects. If a second patient in these safety run-in cohorts at either the 2 or 4 mcg/kg dose level experiences a DLT all treatment and enrollment will be halted to review the data and determine if further clinical evaluation of the combination should be attempted. Treatment will continue for a maximum of 4 cycles or until toxicity (i.e., dose limiting toxicity as found in Section **3.1.1** or toxicity requiring hold as defined in Section **3.3**) or progressive disease.

After the safety of the 4 mcg/kg dose level is established all subsequent patients will be treated with CIVrhIL-15 at the dose of 4 mcg/kg on days 1-5 (120 hours) and avelumab (800mg, by IV) on day 8 and 22 of each 28-day cycle for a maximum of 4 cycles (in the absence of toxicity requiring hold as defined in Section **3.3** or progressive disease).



The standard immune related adverse event (irAE) treatment decision algorithm [66] will be followed to address avelumab related AEs and any patient who requires corticosteroid treatment for irAE will discontinue their rhIL-15 treatment. Since the expected frequency of grade 3 or 4 irAEs with single agent avelumab is extremely low (< 1%), irAE requiring corticosteroid treatment during the first cycle of treatment for the run-in cohort of patients will also be considered a DLT. All patients in the run-in cohort (Cohort 1) must complete their first 28-day cycle of treatment without experiencing a DLT before enrollment into the 4 mcg/kg cohort is initiated.

The efficacy of the combination will be assessed in a Simon two-stage phase II clinical trial scheme that treats a total of minimum 9 or maximum 17 patients at the 4 mcg/kg dose level depending on demonstration of clinical activity in the initial group of patients.

See Section **10.2.1** for details regarding early stopping criteria for the whole trial.

3.1.1 Dose-Limiting Toxicity

A dose-limiting toxicity (DLT) is defined as: any grade 3, 4, or 5 toxicity if not incontrovertibly due to disease progression or an extraneous cause, and deemed possibly, probably or definitely related to IL-15 or avelumab by the PI or designee during the first 28 days of treatment, only for the Safety Run-in cohort (Cohort 1) with the following exceptions.:

3.1.1.1 Hematologic exceptions

- Grade 3 or 4 lymphocytopenia without clinical signs of infection grade 2 or above.
    - rhIL-15 and avelumab will be continued in the event of asymptomatic grade 3 or 4 lymphocytopenia, unless there are clinical signs of significant infection (persistent fevers, labile blood pressure, localized complaints or findings on physical examination, hypoxia or organ dysfunction).
- Grade 3 or 4 neutropenia without clinical signs of infection grade 2 or above.
    - rhIL-15 and avelumab will be continued in the event of grade 3 neutropenia unless there are clinical signs of significant infection, as listed above.
- Grade 3 leukocytosis (WBC > 100,000/mm3) rhIL-15 and avelumab will be continued in the absence of signs of leukostasis or other toxicities possibly related to the expansion of activated cells

3.1.1.2 Non-Hematologic exceptions

- Transient (< 24 hours) grade 3 hypoalbuminemia, hypokalemia, hypomagnesemia, hyponatremia or hypophosphatemia which responds to medical intervention. rhIL-15 and avelumab will be continued while the metabolic abnormalities are corrected by intravenous or oral supplementation
- Non-sustained (< 7 days) grade 3 liver function test (ATL, AST, alkaline phosphatase, total or direct bilirubin) abnormalities deemed unrelated or unlikely related to avelumab, in the absence of clinical signs of hepatic dysfunction (lethargy, confusion, anorexia, pruritus, tremor); for patients with baseline grade 1 elevations, any increase ≥ 10 x baseline will be considered dose-limiting and these patients will be closely monitored for liver function abnormalities.rhIL-15 and avelumab will be continued as long as these abnormalities do not persist for more than 7 days or the patient does not exhibit findings consistent with hepatic toxicity

Management and dose modifications associated with the above adverse events are outlined in Section **3.3**. Occurrence of any of the adverse events listed above after the first 28 days of treatment in the Dose Expansion cohort (Cohort 2) will lead to permanent discontinuation of protocol therapy, but will not be deemed a DLT for purposes of dose escalation. See Section **3.3.3** for more details.

3.1.2 Dose Escalation and DLT Assessment in Safety Run-in Cohorts

Dose escalation in the initial patients treated at the 2 and 4 mcg/kg/day dose levels will proceed according to the following schedule (**Table 5**). Dose escalation will follow the following guidelines (**Table 6**). Dose-limiting toxicity (DLT) is defined above. Each patient will continue treatment at the dose level they were enrolled — there will be no intra-patient dose escalation.

Table 5: IL-15 Dose Escalation Schedule

Dose Level	rhIL-15 (mcg/kg)	Avelumab (mg)
Level 1	2	800
Level 2	4	800
*Doses are stated as exact dose in units (e.g., mg/m^2, mcg/kg, etc.) rather than as a percentage.		

Table 6: Dose Escalation Guidelines

Number of Patients with DLT at a Given Dose Level	Escalation Decision Rule
0 out of 3 for dose level 1	Enter 3 patients at dose level 2.
0 out of 3 for dose level 2	All subsequent patients will be treated at dose level 2 (4mcg/kg). This is the phase 2 dose.
1 out of 3 at either dose level 1 or 2	Enter at least 3 more patients at this dose level. • If 0 of these 3 patients experience DLT at dose level 1, proceed to the dose level 2. • If 0 of these 3 patients experience DLT at dose level 2, all subsequent patients will be treated at dose level 2 (4 mcg/kg)
$\geq$ 2 of 3 or 6 for either dose level 1 or dose level 2	Enrollment and all treatment will be halted. The safety data will be analyzed and the protocol either substantially amended or terminated depending on the results of this safety review and discussion with CTEP and EMD Serono

3.2 DRUG ADMINISTRATION

Each cycle is 28 days (4 weeks). The minimum window between initiation of new cycles is 26 days; a cycle delay due to scheduling or other administrative reasons (i.e., reasons other than toxicity/dose management as defined below) is 7 days. Treatment with rhIL-15 will be given as a continuous IV infusion days 1 through 5 (120 hours) Avelumab had previously been given at a dose of 10 mg/kg, but recently was given permission by the FDA to administer the drug as a flat dose of 800 mg over 60 minutes every 2 weeks. All patients treated in this protocol will receive the flat 800 mg avelumab dose. The diluted avelumab solution will be administered over 60 minutes through an intravenous line containing a sterile, non-pyrogenic, low protein binding in-line filter (pore size of 0.2 micron). Do not co-administer other drugs through the same intravenous line.

rhIL-15 will be given intravenously as a continuous infusion through a central venous (midline) catheter and administered on an inpatient basis during week 1 of the first cycle, and as outpatient during subsequent weeks and cycles unless decided otherwise by the principal investigator based on clinical judgment. Reported adverse events and potential risks are described in Sections **14**.

Appropriate dose modifications for later cycles of treatment are described in Section **3.3**. See **Table 7** below for description of drug regimen.

For a full detailed product description and administration guidelines, see Section **14**. Infusions will be administered via central venous access device (if present; not required to be placed by the study). When administered on an outpatient basis, rhIL-15 will be infused via an ambulatory infusion pump.

Criteria to be eligible for outpatient ambulatory treatment at 2 mcg/kg dose level are:

- no physiologic organ system or fatigue AE > grade 1,
- absence of blood pressure (BP) changes < 20% of baseline or systolic BP < 100 mm Hg,
- more than 5% decline in room air oxygen saturation.

Table 7: Drug Regimen

Agent	Premedications; Precautions	Dose	Route	Schedule
rhIL-15	Premedicate with acetaminophen and/or ibuprofen	** in *** D5W with 0.1% HSA	IV over 24 hours	Days 1-5
Avelumab	Premedicate with acetaminophen and an antihistamine*	** in 250 mL 0.9% or 0.45% NS	IV over 1 hour	Days 8 and 22
* Mandatory for the first four infusions; subsequently based on clinical judgement ** Doses as appropriate for assigned dose level *** Infusion volume of rhIL-15 per calculation in **APPENDIX C**				

3.2.1 Prophylactic and supportive care for IL-15

Patients will be given acetaminophen 500-650mg IV or orally, 30-60 minutes prior to each IL-15 infusion as first line, and ibuprofen 400 or 600mg orally, depending on reactions with acetaminophen as premedication.

3.2.2 Prophylactic and supportive care for avelumab

In order to mitigate infusion related reactions, a premedication with an antihistamine and with acetaminophen 30 to 60 minutes prior to the first 4 infusions of avelumab is mandatory (e.g., 25-50 mg diphenhydramine and 500-650 mg acetaminophen IV or orally). At the discretion of the investigator, famotidine 20mg PO or IV (or other H2 receptor blocker of equivalent efficacy) may also be administered 30 minutes prior to avelumab. Premedication should be administered for subsequent avelumab infusions based upon clinical judgment and presence/severity of prior infusion reactions.

3.2.3 Other modalities or procedures

- Patients will be observed in the day hospital or the inpatient unit for at least 30 minutes after administration of avelumab for potential infusion-related reactions

- Avelumab should be administered in a setting that allows for immediate access to an intensive care unit or equivalent environment and administration of therapy for anaphylaxis, such as the ability to implement immediate resuscitation measures. Steroids (dexamethasone 10 mg), epinephrine (1:1,000 dilution), allergy medications (IV antihistamines), bronchodilators, or equivalents, and oxygen should be available for immediate access.

3.2.4 Clinical Monitoring for the Avelumab Infusion

On Day 8 and Day 22 of Cycle 1 only, vital signs ([VS] blood pressure, pulse, respiratory rate, temperature, oxygen saturation) will be assessed predose of avelumab (within 15 minutes of injection and/or infusion), and then every 15 minutes from the start of avelumab infusion for at least 2 hours. If vital signs are not stable after 2 hours, then continue monitoring every 15 minutes until stable on 2 consecutive repeated measurements and consideration for hospital observation for prolonged vital sign changes or instability if the patient is being treated as an outpatient during subsequent treatment cycles. If a patient requires more than 2 hours of observation during both cycle 1 avelumab treatments, they will be observed for 2 hours with similar vital signs timepoints for cycle 2 day 8 treatment. Once it is clear that a patient can tolerate their Avelumab infusions without any > grade 1 infusion reactions during subsequent treatments, patients will be observed for 30 minutes post completion of their avelumab infusion and vital signs will be obtained per local standard.

Subjects enrolled in this trial must be observed for 2 hours post avelumab infusion in an area with resuscitation equipment and emergency agents. At all times during avelumab and rhIL-15, immediate emergency treatment of an infusion-related reaction or a severe hypersensitivity reaction according to institutional standards must be assured. To treat possible hypersensitivity reactions, for instance, dexamethasone 10 mg and epinephrine in a 1:1000 dilution or equivalents should always be available along with equipment for assisted ventilation. Infusion of avelumab will be stopped in case of Grade $\geq$ 2 hypersensitivity, inflammatory response, or infusion-related reaction.

3.2.5 Clinical Monitoring for the CIV rhIL-15 infusion

The rhIL-15 is given by continuous infusion, and the safety of combined administration will be confirmed by administering Cycle 1 treatment as an inpatient and the patient may continue treatment as an outpatient if they satisfy the criteria listed above in Section **3.2**. It is likely that the majority of patients will receive their CIV rhIL-15 as inpatients and will have regular VS assessment as per nursing unit norms. Patients who experience a decrease in their BP below 100 mmHg or have symptomatic orthostatic changes in the BP will receive NS infusion to increase their BP and alleviate their symptoms. These patients may also receive salt poor albumin (25%) and or transfused packed red blood cells (RBCs) as clinically indicated by their monitoring laboratories. Patients who experience shortness of breath or have decrease in their oxygen saturations below 92% will receive Lasix IV, intermittent low flow oxygen (grade 2 CTC event) and respiratory treatments as clinically indicated to improve their blood oxygen levels. Patients who experience these events will have more frequent VS and clinical assessments as per institutional norms. After Cycle 1 monitoring for dose limiting toxicities, patients may also have brief interruptions (< 2 hours) of their CIV rhIL-15 to allow symptoms to decrease to acceptable levels.

3.2.5.1 Vital Signs during Inpatient treatment

Inpatient: patients will have vital signs (BP, HR, RR, temperature and oxygen saturation) obtained as per inpatient unit norms.

3.2.5.2 Vital Signs for Outpatient treatment

Outpatient: patients will have vital signs (BP, HR, RR, temperature and oxygen saturation) obtained at the time of their visit to have their infusion bag changed.

3.3 DOSE MODIFICATIONS

3.3.1 rhIL-15-specific Adverse Events

Please refer to the Comprehensive Adverse Event and Potential Risk list (CAEPR) for rhIL-15 presented in Section **14.1.8**.

For patients treated later in the phase II dose expansion cohort (Cohort 2) at 4 mcg/kg, CIVrhIL-15 infusion may be interrupted and the dose reduced to 3 mcg/kg for patients who have reversible grade 3 thrombocytopenia, hypoxia, symptomatic hypotension or 3 LFT abnormalities during the CIV rhIL-15 infusion for improved general tolerability. After the safety of the 4 mcg/kg dose level has been established, patients treated in the phase II dose expansion cohort who poorly tolerate the 4 or 3 mcg/kg dose level (significant fatigue or anorexia) will also have the option of further dose reduction to the 2 mcg/kg dose level. Patients who are unable to tolerate the reduced dose of rhIL-15 will discontinue cytokine treatment and may continue treatment with Avelumab.

Dose of rhIL-15 is based on the dose level and patient's weight at the beginning of each cycle and can only be modified for rounding and/or consistency with prior cycles or as specified above, and not for adverse events or renal/hepatic dysfunction. Infusion may continue during correction of electrolyte and other laboratory abnormalities listed in Section **3.1.1**. Infusion may be interrupted for up to two hours each day, but treatment should end 120 (±1) hours after initiation on Day 1.

3.3.2 Avelumab

3.3.2.1 Treatment modifications for symptoms of infusion-related reactions

Table 8: Treatment modifications for infusion-related reactions

NCI-CTCAE Grade	Treatment Modification for Avelumab
Grade 1 – mild Mild transient reaction; infusion interruption not indicated; intervention not indicated.	Decrease the avelumab infusion rate by 50% and monitor closely for any worsening.
Grade 2 – moderate Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (for example, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 h.	Temporarily discontinue avelumab infusion. Resume infusion at 50% of previous rate once infusion-related reaction has resolved or decreased to at least Grade 1 in severity, and monitor closely for any worsening.
Grade 3 or Grade 4 – severe or life-threatening Grade 3: Prolonged (for example, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae. Grade 4: Life-threatening consequences; urgent intervention indicated.	Stop avelumab infusion immediately and disconnect infusion tubing from the subject. Subjects have to be withdrawn immediately from study avelumab and must not receive any further avelumab treatment.
If avelumab infusion rate has been decreased by 50% or interrupted due to an infusion reaction, it must remain decreased for the next scheduled infusion. If no infusion reaction is observed in the next scheduled infusion, the infusion rate may be returned to baseline at the subsequent infusions based on investigator's medical judgment. If hypersensitivity reaction occurs, the subject must be treated according to the best available medical practice.	

IV = intravenous; NCI-CTCAE = National Cancer Institute-Common Terminology Criteria for Adverse Event; NSAIDs = nonsteroidal anti-inflammatory drugs

3.3.2.2 Treatment modifications for immune-related adverse reactions (irAE)

All grading scales in the following tables are according to the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

Table 9: Treatment Modification for Gastrointestinal Immune-related AEs

Gastrointestinal irAEs		
Severity of Diarrhea/Colitis	**Initial Management**	**Follow-up Management**
Grade 1 Diarrhea: increase < 4 stools/day over Baseline; mild increase in ostomy output compared to baseline Colitis: asymptomatic	Continue avelumab therapy Symptomatic treatment (e.g., loperamide)	Close monitoring for worsening symptoms Educate subject to report worsening immediately If worsens: Treat as Grade 2, 3 or 4.

Gastrointestinal irAEs		
Severity of Diarrhea/Colitis	**Initial Management**	**Follow-up Management**
Grade 2 Diarrhea: 4 to 6 stools per day over Baseline; moderate increase in ostomy output compared to baseline; limiting instrumental ADL IV fluids indicated < 24 hours; not interfering with ADL Colitis: abdominal pain; mucus or blood in stool	Withhold avelumab therapy Symptomatic treatment	If improves to Grade ≤ 1: Resume avelumab therapy If persists > 5-7 days or recurs: Treat as Grade 3 or 4.
Grade 3 to 4 Diarrhea (Grade 3): increase of ≥ 7 stools per day over Baseline; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self-care ADL incontinence; IV fluids ≥ 24 h; interfering with ADL Grade 4: Life-threatening consequences; urgent intervention indicated Colitis (Grade 3): severe abdominal pain, medical intervention indicated, peritoneal signs Grade 4: life-threatening, urgent intervention indicated perforation	Withhold avelumab for Grade 3. Permanently discontinue avelumab for Grade 4 or recurrent Grade 3. 1 to 2 mg/kg/day prednisone IV or equivalent Add prophylactic antibiotics for opportunistic infections Consider lower endoscopy	If improves: Continue steroids until Grade ≤ 1, then taper over at least 1 month; resume avelumab therapy following steroids taper (for initial Grade 3). If worsens, persists > 3 to 5 days, or recurs after improvement: Add infliximab 5mg/kg (if no contraindication). Note: infliximab should not be used in cases of perforation or sepsis.

Table 10: Treatment Modifications for Dermatological Immune-related AEs

Dermatological irAEs		
Rash	**Initial Management**	**Follow-up Management**
Grade 1 to 2 Covering ≤ 30% body surface area	Continue avelumab Symptomatic therapy (for example, antihistamines, topical steroids)	If persists > 1 to 2 weeks or recurs: Consider skin biopsy Withhold avelumab Consider skin biopsy Consider 0.5 to 1 mg/kg/day prednisone or equivalent. Once improving, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume avelumab following steroids taper. If worsens: Treat as Grade 3 to 4

Dermatological irAEs		
Rash	**Initial Management**	**Follow-up Management**
Grade 3 to 4 Covering > 30% body surface area; life threatening consequences	Withhold avelumab for Grade 3 Permanently discontinue for Grade 4 or recurrent Grade 3 Consider skin biopsy Dermatology consult 1 to 2 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections	If improves to Grade $\leq$ 1: Taper steroids over at least 1 month and add prophylactic antibiotics for opportunistic infections

Table 11: Treatment Modifications for Pulmonary Immune-related AEs

Pulmonary irAEs		
Pneumonitis	**Initial Management**	**Follow-up Management**
Grade 1 Radiographic changes only	Consider withholding avelumab Monitor for symptoms every 2 to 3 days Consider Pulmonary and Infectious Disease consults	Re-assess at least every 3 weeks If worsens: Treat as Grade 2 or Grade 3 to 4
Grade 2 Mild to moderate new symptoms	Withhold avelumab Pulmonary and Infectious Disease consults Monitor symptoms daily, consider hospitalization 1 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Consider bronchoscopy, lung biopsy	Re-assess every 1 to 3 days If improves: When symptoms return to Grade $\leq$ 1, taper steroids over at least 1 month and then resume avelumab following steroids taper If not improving after 2 weeks or worsening: Treat as Grade 3 to 4
Grade 3 or 4 Grade 3:Severe new symptoms; New / worsening hypoxia; Grade4: Life-threatening	Permanently discontinue avelumab Hospitalize Pulmonary and Infectious Disease consults 1 to 2 mg/kg/day prednisone o equivalent Add prophylactic antibiotics for opportunistic infections Consider bronchoscopy, lung biopsy	If improves to Grade $\leq$ 1: Taper steroids over at least 1 month If not improving after 48 hours or worsening: Add additional immunosuppression (for example, infliximab, cyclophosphamide, IV immunoglobulin, or mycophenolate mofetil)

Table 12: Treatment Modifications for Hepatic Immune-related AEs

Hepatic irAEs		
Liver test elevation	**Initial Management**	**Follow-up Management**
Grade 1 Grade 1 AST or ALT > ULN to 3.0 x ULN and / or total bilirubin > ULN to 1.5 x ULN	Continue avelumab	Continue liver function monitoring If worsens: Treat as Grade 2 or 3 to 4
Grade 2 AST or ALT > 3.0 to ⩽ 5 x ULN and/or total bilirubin > 1.5 to ⩽ 3 x ULN	Withhold avelumab Increase frequency of monitoring to every 3 days	If returns to Grade ≤1: Resume routine monitoring, resume avelumab If elevations persist > 5 to 7 days or worsen: Treat as Grade 3 or 4
Grade 3 to 4 AST or ALT > 5 x ULN and/or total bilirubin > 3 x ULN	Permanently discontinue avelumab Increase frequency of monitoring to every 1 to 2 days 1 to 2 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Consult gastroenterologist/ hepatologist Consider obtaining MRI/CT scan of liver and liver biopsy if clinically warranted	If returns to Grade ≤ 1: Taper steroids over at least 1 month and add prophylactic antibiotics for opportunistic infections If does not improve in > 3 to 5 days, worsens or rebounds: Add mycophenolate mofetil 1 gram (g) twice daily If no response within an additional 3 to 5 days, consider other immunosuppressants per local guidelines

Table 13: Treatment Modifications for Renal Immune-related AEs

Renal irAEs		
Creatinine Increase	**Initial Management**	**Follow-up Management**
Grade 1 Creatinine increased > ULN to 1.5 x ULN	Continue avelumab	Continue renal function monitoring If worsens: Treat as Grade 2 or 3 to 4
Grade 2 to 3 Creatinine increased > 1.5 and ⩽ 6 x ULN	Withhold avelumab Increase frequency of monitoring to every 3 days 1 to 2 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections Consider renal biopsy	If returns to Grade ≤1: Taper steroids over at least 1 month, and resume avelumab following steroids taper. If worsens: Treat as Grade 4.

Renal irAEs		
Creatinine Increase	**Initial Management**	**Follow-up Management**
Grade 4 Creatinine increased > 6 x ULN	Permanently discontinue avelumab Monitor creatinine daily 1 to 2 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections Consider renal biopsy Nephrology consult	If improves to Grade $\leq$ 1: Taper steroids over at least 1 month

Table 14: Treatment Modifications for Cardiac Immune-related AEs

Cardiac irAEs		
Myocarditis	**Initial Management**	**Follow-up Management**
New onset of cardiac signs or symptoms and / or new laboratory cardiac biomarker elevations (e.g., troponin, CK-MB, BNP) or cardiac imaging abnormalities suggestive of myocarditis	Withhold avelumab. Hospitalize. In the presence of life threatening cardiac decompensation, consider transfer to a facility experienced in advanced heart failure and arrhythmia management. Cardiology consult to establish etiology and rule out immune- mediated myocarditis. Guideline based supportive treatment as per cardiology consult.* Consider myocardial biopsy if recommended per cardiology consult.	If symptoms improve and immune-mediated etiology is ruled out, re-start avelumab. If symptoms do not improve/worsen, viral myocarditis is excluded, and immune-mediated etiology is suspected or confirmed following cardiology consult, manage as immune-mediated myocarditis.
Immune-mediated myocarditis	Permanently discontinue avelumab. Guideline based supportive treatment as appropriate as per cardiology consult.* 1 to 2 mg/kg/day. prednisone or equivalent Add prophylactic antibiotics for opportunistic infections.	Once improving, taper steroids over at least 1 month. If no improvement or worsening, consider additional immunosuppressants (e.g., azathioprine, cyclosporine A)
*Local guidelines, or e.g., European Society of Cardiology or American Heart Association guidelines European Society of Cardiology guidelines website: https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines American Heart Association guidelines website: http://professional.heart.org/professional/GuidelinesStatements/searchresults.jsp?q=&y=&t=1001		

Table 15: Treatment Modifications for Endocrine Immune-related AEs

Endocrine irAEs		
Endocrine disorder	**Initial Management**	**Follow-up Management**
Grade 1 or Grade 2 endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, type I diabetes mellitus)	Continue avelumab Endocrinology consult if needed Start thyroid hormone replacement therapy (for hypothyroidism), anti-thyroid treatment (for hyperthyroidism), corticosteroids (for adrenal insufficiency) or insulin (for Type I diabetes mellitus) as appropriate. Rule-out secondary endocrinopathies (i.e., hypopituitarism / hypophysitis)	Continue hormone replacement/suppression and monitoring of endocrine function as appropriate.
Grade 3 or Grade 4 endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, type I diabetes mellitus)	Withhold avelumab Consider hospitalization Endocrinology consult Start thyroid hormone replacement therapy (for hypothyroidism), anti-thyroid treatment (for hyperthyroidism), corticosteroids (for adrenal insufficiency) or insulin (for type I diabetes mellitus) as appropriate. Rule-out secondary endocrinopathies (i.e., hypopituitarism / hypophysitis)	Resume avelumab once symptoms and/or laboratory tests improve to Grade ≤ 1 (with or without hormone replacement/suppression). Continue hormone replacement/suppression and monitoring of endocrine function as appropriate.
Hypopituitarism/Hypophysitis (secondary endocrinopathies)	If secondary thyroid and/or adrenal insufficiency is confirmed (i.e., subnormal serum FT4 with inappropriately low TSH and/or low serum cortisol with inappropriately low ACTH) : • Refer to endocrinologist for dynamic testing as indicated and measurement of other hormones (FSH, LH, GH/IGF-1, PRL, testosterone in men, estrogens in women) • Hormone replacement/suppressive therapy as appropriate • Perform pituitary MRI and visual field examination as indicated If hypophysitis confirmed: • Continue avelumab if mild symptoms with normal MRI. Repeat the MRI in 1 month • Withhold avelumab if moderate, severe or life-threatening symptoms of hypophysitis and/or abnormal MRI. Consider hospitalization. Initiate corticosteroids (1 to 2 mg/kg/day prednisone or equivalent) followed by corticosteroids taper during at least 1 month. • Add prophylactic antibiotics for opportunistic infections.	Resume avelumab once symptoms and hormone tests improve to Grade ≤ 1 (with or without hormone replacement). In addition, for hypophysitis with abnormal MRI, resume avelumab only once shrinkage of the pituitary gland on MRI/CT scan is documented. Continue hormone replacement/suppression therapy as appropriate.

Table 16: Treatment Modifications for Other Immune-related AEs

Other irAEs (not described above)		
Grade of other irAEs (NCI CTCAE v5)	**Initial Management**	**Follow-up Management**
Grade 2 or Grade 3 clinical signs or symptoms suggestive of a potential irAE	Withhold avelumab pending clinical investigation	If irAE is ruled out, manage as appropriate according to the diagnosis and consider re-starting avelumab If irAE is confirmed, treat as Grade 2 or 3 irAE.
Grade 2 irAE **Or** **first occurrence of Grade 3 irAE**	Withhold avelumab 1 to 2 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections Specialty consult as appropriate	If returns to Grade $\leq$ 1: Taper steroids over at least 1 month, and resume avelumab following steroids taper.
Recurrence of same Grade 3 irAEs	Permanently discontinue avelumab 1 to 2 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections Specialty consult as appropriate	If returns to Grade $\leq$ 1: Taper steroids over at least 1 month
Grade 4	Permanently discontinue avelumab 1 to 2 mg/kg/day prednisone or equivalent and/or other immunosuppressant as needed. Add prophylactic antibiotics for opportunistic infections Specialty consult	If improves to Grade $\leq$ 1: Taper steroids over at least 1 month
Requirement for 10 mg per day or greater prednisone or equivalent for more than 12 weeks for reasons other than hormonal replacement for adrenal insufficiency **Persistent Grade 2 or 3 irAE lasting 12 weeks or longer**	Permanently discontinue avelumab Specialty consult	

Abbreviations: ACTH=adrenocorticotropic hormone; ADL=activities of daily living; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BNP=B-type natriuretic peptide; CK-MB=creatine kinase MB; CT= computed tomography; FSH=follicle-stimulating hormone; GH=growth hormone; IGF-1=insulin-like growth factor 1; irAE=immune related adverse event; IV=intravenous; LH=luteinizing hormone; MRI=magnetic resonance

imaging; NCI CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events; PRL=prolactin;T4=thyroxine; TSH=thyroid stimulating hormone; ULN=upper limit of normal.

3.3.3 Unacceptable Toxicity

Occurrence of any of the adverse events listed in Section **3.1.1** after the first 28 days of treatment in the Dose Expansion cohort (Cohort 2) will lead to permanent discontinuation of protocol therapy, but will not be deemed a DLT for purposes of dose escalation. Any patient who requires corticosteroid treatment for an avelumab related irAE will have their rhIL-15 discontinued regardless of their perceived tolerance of the cytokine. Patients may continue single agent avelumab after halting rhIL-15 treatment if considered appropriate in the standard avelumab irAE decision algorithm.

3.4 Study Intervention Compliance

Adherence to the protocol will be verified by reviewing the Medical Administration Record (MAR) section of the medical record, which will serve as source documentation.

3.5 On Study Evaluations

Prior to avelumab administration (Day 8 and 22), pre-dose assessments must be performed (up to 3 days prior). After Cycle 1, pre-dose assessments may be performed up to 3 days prior to a cycle except where otherwise noted. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy. The results from all procedures/tests must be reviewed prior to initiation of each cycle of treatment for consideration of dose modifications and delay of therapy.

Treatment with rhIL-15 and avelumab will continue for 4 cycles or until disease progression, unacceptable treatment-related toxicity or other reasons outlined in Section **3.9.1**.

Refer to the Study Calendars (Section **APPENDIX F**) for a complete list of procedures to be performed at each scheduled study visit. See also Section **5** for all samples to be collected for correlative research. During treatment, it is expected that all laboratory and clinical assessments be conducted at the NIH (including post-treatment imaging evaluations); results from outside NIH will only be accepted at the discretion of the investigator.

3.6 Post-Treatment Evaluations

Post treatment evaluations (i.e., End of Treatment Visit) will be performed approximately 30 days after the last dose of protocol 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, if possible. If the patient cannot return to the Clinical Center for this visit, a request will be made to have a local physician or laboratory collect a CBC with differential and send the results. If this is not possible, patients may be assessed by telephone or email for symptoms.

Unless otherwise noted, follow-up will occur at the following time point: every 60 days (± 7 days) for 6 months; then every 90 days (± 14 days) for 2 years; then every six months (± 28 days) for the duration of the study until the start of a new anti-neoplastic therapy, disease progression, death or end of study. Any other evaluations and tests should be performed as clinically indicated.

Upon disease progression or initiation of other anti-cancer therapy, contact will be for survival only until the subject is off study (i.e., every 3 months [±4 weeks]) for the duration of the study. See Study Calendar (Section **APPENDIX F**) for additional information. Any adverse events

which are present at the time of discontinuation should be followed in accordance with the safety requirements.

Patients who are removed from study before completing protocol treatment will be followed until completion of the Safety Follow-up Visit or until death, whichever occurs first. Patients removed from study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

3.6.1 Safety Follow-Up Visit

The safety follow-up visit should occur 30 days (±7 days) after the last dose of trial treatment, or before the initiation of a new anti-cancer treatment, whichever comes first. Required testing is as noted in the Study Calendars (Section **APPENDIX F**). All AEs that occur prior to the Safety Follow-Up Visit should be recorded. Patients with an ongoing, treatment-related AE of Grade > 1 will be followed until the resolution of the AE to Grade 0-1, stabilization of the AE in the opinion of the investigator, or until the beginning of a new anti-neoplastic therapy, whichever occurs first. SAEs that occur within 30 days of the end of treatment or before initiation of a new anti-cancer treatment should also be followed and recorded.

3.6.2 Extended Safety Follow-up

Given the potential risk for delayed immune-related toxicities, safety follow-up must be performed up to 90 (+14) days after the last dose of avelumab administration. This may be performed either via a clinic visit or via a telephone call/email with subsequent clinic visit requested in case any concerns are noted during the telephone call/email.

3.6.3 Follow-Up Visits- Prior to Disease Progression

Patients who complete trial treatment or discontinue treatment without evidence of disease progression will move into the Follow-up Phase and may be assessed every 60 days (± 7 days) for 6 months; then every 90 days (± 14 days) for 2 years; then every six months (± 28 days) for the duration of the study after finishing treatment by radiologic imaging or other clinical assessments 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 If the patient cannot return to the Clinical Center for any of these visits, a request will be made to have a local physician or laboratory collect a CBC with differential and send the results. If this is not possible, patients may be assessed by telephone or email for symptoms.

3.6.4 Follow-Up Visits – Survival/Post-Disease Progression

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 (e.g., phone, email, etc.; in-person visit not required) at least every 3 months for the duration of the study to collect information on new anti-cancer treatments received and to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first (see Study Calendar).

3.7 STUDY CALENDAR

See **APPENDIX F.**

3.8 COST AND COMPENSATION

3.8.1 Costs

NIH does not bill health insurance companies or participants for any research or related clinical care that participants receive at the NIH Clinical Center. If some tests and procedures performed outside the NIH Clinical Center, participants may have to pay for these costs if they are not covered by insurance company. Medicines that are not part of the study treatment will not be provided or paid for by the NIH Clinical Center.

3.8.2 Compensation

Subjects will not be compensated.

3.8.3 Reimbursement

On this study, the NCI will cover the cost for some of the expenses. Some of the costs may be paid directly by the NIH and some may be reimbursed to the subject. Someone will work with subjects to provide more information

3.9 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

Prior to removal from study, effort must be made to have all patients complete a safety visit approximately 30 days following the last dose of study therapy. Additional safety visits and follow-up will continue as per Section **3.6**.

3.9.1 Criteria for removal from protocol therapy

In the absence of treatment delays due to adverse event(s), treatment may continue for 4 cycles or until one of the following criteria applies. Patients who meet the following criteria should be discontinued from protocol therapy:

- Completion of protocol therapy (i.e., up to 4 cycles)
- Clinical or Disease progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable toxicities as listed in Section **3.1.1** or those toxicities listed in Section **3.3** that require treatment to be stopped.
- Subject's request to withdraw from protocol therapy
- Investigator's decision to withdraw the patient
- Subject's non-compliance with trial treatment or procedure requirements that requires removal in the opinion of the PI
- Pregnancy
- Study is cancelled for any reason
- The drug manufacturer can no longer proved the study agent

3.9.2 Off-Study Criteria

- Subject requests to be withdrawn from study
- Subject is lost to follow-up*
- Death
- Study is cancelled for any reason

3.9.3 Lost to Follow-up

* A participant will be considered lost to follow-up if he or she fails to return for 3 consecutive scheduled visits without good cause and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant within 1-3 business days (to take into account the weekend) to reschedule the missed visit, and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

4 CONCOMITANT MEDICATIONS/MEASURES

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for one of these or other medications or vaccinations specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required.

For premedication and supportive care measures, see Section **3.2.1**, **3.2.2** and **3.2.3**.

4.1 ACCEPTABLE MEDICATIONS

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

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

4.2 PROHIBITED MEDICATIONS

Patients are prohibited from receiving the following therapies during treatment on this trial:

- Other therapy for the disease under study not specified in this protocol, unless specifically noted as permitted
- Investigational agents other than rhIL-15 and avelumab
- Radiation therapy
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following:

measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine and Flu Mist.

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

5 CORRELATIVE STUDIES

5.1 SUMMARY

This study will attempt to use rhIL-15 to increase NK cell number and activity, thereby enhancing the ADCC of avelumab in treatment of patients with relapsed and refractory metastatic PD-L1+ ccRCC. ADCC capacity of ex vivo PBMCs will be tested on PD-L1-expressing cell lines before, during and after protocol treatment. Differences in immune cell subsets associated with administration will be followed throughout treatment to both study the effects of combined rhIL-15/avelumab therapy on the immune system, and to identify potential biomarkers that would be predictive of response.

Sample	**Collection Details***	**Time Points**						**Supervising Laboratory/ Investigator**
		Baseline	C1 D8	C1 D22	C2-4 D1	C2-4 D8	Follow up[#]	
Blood Samples								
Lymphocyte subset testing	• 2 x 10mL K_2EDTA (lavender-top) tubes	X	X	(X)		(X)	(X) [1]	Immunology section, NIH CC
ADCC of avelumab	• 3 x 10mL sodium heparin green-top tubes	(X)[2]	(X)[2]			(X) [2]		Waldmann (Leidos CSL)
Circulating tumor DNA, plasma banking	• 1 x 10mL K_2EDTA tube • 1 x 10mL Streck/BCT tube	X	(X)			(X)	X[3]	(Leidos CSL)
Anti-IL-15 antibodies	• 1 x 4mL SST tube	X			X		X[1]	(Leidos CSL)
Tissue Samples								
Tissue immune cell subsets by Immunohistochemistry	• Two core biopsy samples in formalin	X[**]		(X)[***]	(X)[***]		(X)	(Laboratory of Pathology)

			Time Points	Supervising
(X) = Optional *Tubes/media may be adjusted at the time of collection based upon materials available or to ensure the best samples are collected for planned analyses. ** Pretreatment tumor biopsy sample: may use the archival tissue or the freshly obtained tumor biopsy used to assess PD-L1 expression for eligibility *** The on-treatment tumor biopsy may be obtained anywhere between cycle 1 day 22 and cycle 2 day 4 at whichever time is most expedient for the patient and Interventional Radiology #Subjects who discontinue treatment for a reason other than disease progression and who do not start new treatment should continue to have study bloods collected at the scheduled time points. [1] At the end of treatment only. [2] For ADCC of avelumab, Baseline and C1D8 samples should be collected for at least one patient per dose level, and for at least three patients at the MTD; C2-6 samples may be collected at the discretion of the PI but are not required. [3] At each follow-up visit prior to disease progression, as specified in Section **3.6.3**				

5.2 SAMPLE COLLECTION AND PROCESSING

5.2.1 Blood Samples

All blood samples will be drawn by NIH Clinical Center phlebotomy, outpatient clinic, or day hospital staff

5.2.2 Summary

The planned analyses described below may be done on leftover and/or shared sample portions from the respective laboratories, as needed. In addition to the prospectively collected samples below, leftover portions of samples sent for routine laboratory testing (e.g., plasma from CBC/hematologies) may also be retrieved for research tests prior to being discarded. The planned prospective analyses are identified below; laboratories may share resources or collaborate on analyses, if appropriate.

Portions of all samples may be banked for future research analyses; prospective consent will be obtained during the informed consent process.

The blood drawing limits for research purposes are as follows:

- For adult subjects: The amount of blood that may be drawn from adult patients for research purposes shall not exceed 10.5 mL/kg or 550 mL, whichever is smaller, over any eight-week period.

Unless otherwise noted, Clinical Research personnel will use courier or escort service to arrange delivery of samples to destinations listed in subsections below.

5.2.3 Blood Samples

5.2.3.1 Lymphocyte subset testing by flow cytometry (FACS)

- Whole blood will be collected for each timepoint in 10mL EDTA tubes that are gently invert tubes 8-10 times immediately after collection to thoroughly mix the sample to prevent clotting and loss of mononuclear cells intended to be analyzed.
- Labels will be affixed to these tubes with the patient's name, date of birth, date and time of the blood draw by the hospital staff who obtained the samples.

- One each of the 2 EDTA tubes drawn at the timepoints summarized in table 2 will be delivered to 2 separate locations:
    - Routine LYMB flow cytometry panels will be transported to Immunology Lab, NIH Clinical Center Bldg. 10/ Room 2C410 for analysis. If the Immunology Section Laboratory is unable to perform the complete LYMB flow cytometry panels for the specified timepoint, the analysis maybe omitted or replaced with the more limited "TBNK panel."
    - Clinical Research Staff will arrange for the cells collected for more extensive bulk flow cytometry studies performed at the completion of all subjects' protocol treatments to be picked up by the Frederick courier from either Phlebotomy or the 12 Floor Outpatient Clinic (OP12) and conveyed to the CLS laboratory Frederick for controlled freezing and storage .

5.2.3.2 Antibody-dependent cell cytotoxicity (ADCC) of avelumab

- Whole blood will be collected for each timepoint in 10mL sodium heparin tubes that are gently invert tubes 8-10 times immediately after collection .
- Labels will be affixed to these tubes with the patient's name, date of birth, date and time of the blood draw by the hospital staff who obtained the samples.
- Clinical Research personnel will arrange for these samples to be delivered to Clinical Support Laboratory, Leidos Biomedical Research, Inc.in Frederick, MD, for processing per established laboratory techniques storage, and batch analysis by the Waldmann Laboratory.

5.2.3.3 Cell-free DNA (cfDNA), and circulating tumor DNA (ctDNA) and plasma banking

- Collect 10 mL of blood in one cell-free DNA (e.g., Streck BCT/collection tubes) and 10 mL of blood in one K2EDTA tube; gently invert the tubes 8-10 times immediately after collection.
- Labels listing the patient's name, date of birth, date and time of the blood draw will be affixed to all the tubes by the staff person who obtained the samples. each).
- Clinical Research personnel will arrange for these samples to be delivered to Clinical Support Laboratory, Leidos Biomedical Research, Inc.in Frederick, MD for sample processing per established laboratory techniques and maintained within standard operating procedures in the laboratory.

5.2.3.4 Anti-IL-15 antibody testing

- Collect blood in a 4mL SST tube; gently invert tubes 8-10 times immediately after collection.
- Clinical Research personnel will arrange for these samples to be delivered to Clinical Support Laboratory, Leidos Biomedical Research, Inc.in Frederick, MD, for storage and further analysis.

- Samples will be batch processed and analyzed per the procedure outlined in **APPENDIX D** after the last patient has been enrolled and completed treatment, or sooner if there is clinical suspicion for anti-IL-15 antibody formation.

5.2.4 Tissue Samples

5.2.4.1 PDL-1 testing for immunohistochemistry (IHC)

- If a prospective patient's tumor has not already assessed for PD-L1 expression as listed in the eligibility Section **2.1** archival block(s) or slides (i.e., at least 15 unstained slides, 5-microns) is/are required at screening. Patients with prior tumor biopsies performed at NIH or outside institutions may make specimen blocks available to the NCI Pathology Department for analysis. If no prior biopsies are available at the time of screening, a punch or core biopsy of an appropriate easily accessible tumor deposit will be performed during screening period to confirm PDL-1 status for eligibility. Patients with lymph node and/or visceral involvement will undergo an 18g core biopsy performed by the Department of Radiology and Imaging Sciences' Interventional Radiologists (IR).
- Prior specimen blocks will be sent to NCI Pathology Department via FedEx. For patients with no prior samples who undergo biopsy as part of screening, fresh samples will be placed in transport saline or 10% formalin PBS and sent to the Department of Laboratory Medicine (DLM)/ NCI Laboratory of Pathology (LP) (Section **5.1** and **5.2**) for concurrent routine histologic analysis and reporting and IHC testing for PD-L1 expression by tumor area Lab).

5.2.4.2 Optional Tissue Samples

- Archival block(s)/ slides or fresh tumor tissue that was obtained to determine eligibility expression of PD-L1 will also be used for pre-treatment IHC analysis of lymphocyte subsets and other immune molecules as described below in section **5.3.5**. If no prior sample is available, core biopsies will be performed during the screening period by IR and the specimens will be transported to NCI pathology as described previously in section **5.2.4.1**.
- The optional, on-treatment research biopsy will be obtained during the period from cycle 1 day 22 to cycle 2 day 4 and sent to the Laboratory of Pathology as described above in section **5.2.4.1**. and under the analyses described below in section **5.3.5**.

5.3 BIOMARKER AND RESEARCH METHODS

The technology platforms that are able to interrogate genomic structure and function are constantly in flux; therefore, the exact nature of the methodologies that will be employed will be assessed at the time that the samples are collected and ready for analysis. The protocol will be amended at that time, if needed, to describe the intended techniques prior to initiating the analyses

The following are technologies that are currently in use for each planned analysis:

5.3.1 Flow Cytometry of Peripheral Blood Lymphocytes

Immunohistochemical (IHC) analyses of tumor tissue samples, including but not necessarily limited to CD2, CD3, CD4, CD5, CD7, CD8, CD14, CD16, CD20, CD25, CD38, CD45RA,

CD45RO, CD56, CD62L, CD69, CD79a/CD79b, CD122, Foxp3, perforin, gamma/delta, CXCR3, CCR4, and NKG2D.

5.3.2 Immune Subset Analysis

Peripheral blood mononuclear cells (PBMC) will be assessed using multiparameter flow cytometry listed in section **5.3.1** and used to define cytotoxic CD8+ T-cells, Tregs, T-effector cells, Th1, Th2 and Th17+ CD4+ T-cells, NK cells and subsets, monocyte subsets, MDSC subsets. Assessment may include functional markers, i.e. PD-1, Tim-3, CTLA-4, PD-L1, HLA-DR, Ki67 and/or CD40.

5.3.3 ADCC Analysis

Peripheral blood mononuclear cells (PBMCs) should be isolated by Ficoll-Hypaque Density Gradient Centrifugation. The viable cells should be viably frozen and stored in liquid nitrogen. The ADCC assay will be performed on the same occasion for all samples of a given patient. Vials of frozen cells will be thawed using standard procedures 18 hours before the assay in accord with our experience with normal donors. 1.5 million of patient's PBMCs obtained before and on day 15 following IL-15 injection will be tested in aliquots as follows:

- Tested alone
- Tested with untreated PD-L1-expressing Raji cells, and with the Raji cells coated with avelumab for 5 hours.
- In addition, we may utilize an ATL cell line in addition to Raji cells. These cell populations will be stained with CD107, CD3, CD56, and CD94.

5.3.4 cfDNA/ctDNA

Since the methods of molecular monitoring in the peripheral blood is an emerging field with numerous technologies under development, the storage of peripheral blood mononuclear cells (PBMC), serum, and plasma will all be performed allowing for future comparison of the different compartments for analytes that include cell-free circulating tumor DNA (ctDNA), and RNA sequencing of circulating tumor cells. Studies to be performed on these samples include: cfDNA/ctDNA for liquid genotyping as a non-invasive dynamic monitoring of disease as well as monitoring for individual molecular aberrations that may be present for individual patients. Changes in the level of ctDNA have been shown to correlate with response to tyrosine kinase inhibitor (TKI) treatment for mRCC and will be quantitated to assess response to therapy [81, 82]. Analysis of ctDNA for characteristic mutations present in ccRCC will also be performed [83]. Additional samples will be stored for later bulk analysis of chromosomal copy number instability (CNI) which recently has been identified as a possible surrogate marker of response to immunotherapy [84, 85] and to analyze for loss of function PBrm1 mutations that was recently reported to be associated with increased clinical benefit in ccRCC patients after ICI treatment [86].

5.3.5 Immunohistochemical Analyses of Optional Tissue Samples

Standard H&E pathologic examination and IHC listed in section **5.3.1** for peripheral blood lymphocytes, will also be performed on the tissue samples obtained to characterize the *in situ* immune response. In addition, other important immune molecules such as PD-1, Fas, FasL, KIR2DL1, NKG2A, NKG2D, TIGID will be performed using established procedures for the Laboratory of Pathology. In situ cytokine analysis (e.g., IL-6, IL-10, interferon beta, TNF-alpha) using established laboratory procedures.

5.3.6 Other Analyses

Testing for anti-IL-15 antibodies will be on a regular basis or in bulk to determine if any subject developed anti-IL-15 antibodies that may have affected their response to therapy. Since no subject's treatment with CIV rhIL-15 [70, 87]have developed antibodies to the cytokine, this test is no longer required prior to the administration of any cycle of treatment.

5.3.7 Future Use

Any blood, tissue, or other products or portions leftover from other analyses will be stored for future research.

5.4 SAMPLE STORAGE, TRACKING, AND DISPOSITION

5.4.1 General

Samples will be ordered in CRIS and tracked through a Clinical Trial Data Management system. Should a CRIS screen not be available, the CRIS downtime procedures will be followed. Samples will not be sent outside NIH without appropriate approvals and/ or agreements, if required.

All specimens obtained in the protocol are used as defined in the protocol. Any specimens that are remaining at the completion of the protocol will be stored in the conditions described below. The study will remain open so long as sample or data analysis continues. Samples from consenting subjects will be stored until they are no longer of scientific value or if a subject withdraws consent for their continued use, at which time they will be destroyed.

If the patient withdraws consent the participant's data will be excluded from future distributions, but data that have already been distributed for approved research use will not be able to be retrieved.

The PI will record any loss or unanticipated destruction of samples as a deviation. Reporting will be per the requirements of section **7.2.1**

All samples that are noted in Section **5.1** to be analyzed by the Waldmann Laboratory will first be processed and stored at Clinical Support Laboratory, Leidos Biomedical Research, Inc. in Frederick, MD, as per Section **5.4.2**.

5.4.2 Clinical Support Laboratory, Leidos Biomedical Research, Inc. in Frederick, MD

The Clinical Support Laboratory, Leidos Biomedical Research, Inc.-Frederick, processes and cryopreserves samples in support of IRB-approved, NCI clinical trials. The laboratory is CLIA certified for anti-IL15 and certain cytokine measurements and all laboratory areas operate under a Quality Assurance Plan with documented Standard Operating Procedures that are reviewed annually. Laboratory personnel are assessed for competency prior to being permitted to work with patient samples. Efforts to ensure protection of patient information include:

- The laboratory is located in a controlled access building and laboratory doors are kept locked at all times. Visitors to the laboratory are required to be accompanied by laboratory staff at all times.
- Hard copy records or electronic copies of documents containing patient information are kept in the locked laboratory or other controlled access locations.
- An electronic database is used to store information related to patient samples processed by the laboratory.
- The database resides on a dedicated program server that is kept in a central, locked computer facility.

- The facility is supported by two IT specialists who maintain up to date security features including virus and firewall protection.
- Program access is limited to specified computers as designated by the laboratory director. Each of these computers has a password restricted login screen.
- The database sample entry program itself is accessed through a password protected entry screen.
- Upon specimen receipt each sample is assigned a unique, sequential laboratory accession ID number. All products generated by the laboratory that will be stored either in the laboratory freezers or at a central repository facility are identified by this accession ID.
- Inventory information will be stored at the vial level and each vial will be labeled with both a sample ID and a vial sequence number.
- Vial labels do not contain any personal identifier information.
- Samples are stored inventoried in locked laboratory freezers and are routinely transferred to the NCI-Frederick repository facilities for long term storage.
- Access to stored clinical samples is restricted. Investigators establish sample collections under "Source Codes" and the investigator responsible for the collections, the protocol Principal Investigator, specifies who has access to the collection.
- Specific permissions will be required to view, input or withdraw samples from a collection. Sample withdrawal requests submitted to approved laboratory staff by anyone other than the repository source code owner are submitted to the source code owner for approval. The repository facility will also notify the Source Code holder of any submitted requests for sample withdrawal.
- It is the responsibility of the Source Code holder (the NCI Principal Investigator) to ensure that samples requested and approved for withdrawal are being used in a manner consistent with IRB approval.
- The Clinical Support Laboratory does perform testing services that may be requested by clinical investigators including, but not limited to, immunophenotyping by flow cytometry and cytokine testing using ELISA or multiplex platforms.
- When requests are submitted by the NCI investigator for shipment of samples outside of the NIH it is the policy of the laboratory to request documentation that a Material Transfer Agreement is in place that covers the specimen transfer. The laboratory does not provide patient identifier information as part of the transfer process but may, at the discretion of the NCI investigator, group samples from individual patients when that is critical to the testing process.
- The NCI investigator responsible for the sample collection is responsible for ensuring appropriate approvals and/ or agreements are in place, if required, prior to requesting the laboratory to ship samples outside of the NIH.

5.4.3 Hematopathology Section of the Laboratory of Pathology (Tissue samples)

Archival and/or freshly collected and processed tumor tissue may be stored in the Hematopathology Section of Laboratory of Pathology until ready for planned and/or future research assays if the patient has agreed to allowing specimens to be used in future research studies. IRB approval will be obtained before using any samples to conduct studies that are not described

within this protocol. Samples will be stored under conditions appropriate to the type of sample and processing (e.g., ambient or frozen).

Tissue that is given to the technician will be assigned an accession number (HP#) in the HP Case Logbook; sample tracking also takes place with a FileMaker Pro data base called HP Patient Information and Specimen Inventory. A Patient background sheet may be filled out and filed with any accompanying paperwork, with final reports and any supplemental reports that follow added as completed.

6 DATA COLLECTION AND EVALUATION

6.1 DATA COLLECTION

6.1.1 Summary

The PI will be responsible for overseeing entry of data into an in-house password protected electronic system (C3D) and ensuring data accuracy, consistency and timeliness. The principal investigator, associate investigators/research nurses and/or a contracted data manager will assist with the data management efforts. Primary and final analyzed data will have identifiers so that research data can be attributed to an individual human subject participant.

All adverse events (AEs), including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed until return to baseline or stabilization of event.

Document AEs from the first study intervention, Study Day 1, through 30 days after the last dose of study treatment. After 30 days, only adverse events which are serious and related to the study intervention need to be recorded.

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

Loss or destruction of data: Should we become aware that a major breach in our plan to protect subject confidentiality and trial data has occurred, this will be reported expeditiously per requirements in section **7.2.1**.

6.1.2 Data Collection/Reporting Exceptions

6.1.2.1 Abnormal Laboratory Values

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

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

6.2 DATA SHARING PLANS

6.2.1 Human Data Sharing Plan

What data will be shared?

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

_X_ Coded, linked data in an NIH-funded or approved public repository.

_X_ Coded, linked data in another public repository

_X_ Coded, linked data in BTRIS (automatic for activities in the Clinical Center)

_X_ Identified or coded, linked data with approved outside collaborators under appropriate agreements.

How and where will the data be shared?

Data will be shared through:

_X_ An NIH-funded or approved public repository. Insert name or names: ClinicalTrials.gov, dbGaP.

_X_ BTRIS (automatic for activities in the Clinical Center)

_X_ Approved outside collaborators under appropriate individual agreements.

_X_ Publication and/or public presentations.

When will the data be shared?

_X_ Before publication.

_X_ At the time of publication or shortly thereafter.

6.2.2 Genomic Data Sharing Plan

The NIH Genomic Data Sharing plan does not apply to this protocol.

6.3 RESPONSE CRITERIA

6.3.1 Response Assessments

Tumor response will be assessed radiographically after cycle 2 and 4 treatments are completed by the investigator using the Immune-Modified Response Evaluation Criteria In Solid Tumors, i.e., imRECIST criteria [88] for Immune-related Best Overall Response (irBOR, Section **6.4.1**) will be derived based on reported lesion responses at different evaluation time points from the first trial treatment administration until immune-related disease progression per irRECIST [88] according to the following rules:

- irCR = at least two radiographic determinations of CR at least 4 weeks apart and before irPD
- irPR = at least two radiographic determinations of PR or better at least 4 weeks apart and before irPD (and not qualifying for an irCR)
- irSD = at least one radiographic assessment of SD (or better) ≥ 6 weeks after the first trial treatment administration and before irPD (and not qualifying for irCR or irPR).
- irPD = at least two consecutive radiographic determinations of PD at least 4 weeks apart.

Only tumor assessments performed before the start of any further anti-cancer treatment will be considered in the assessment of irBOR.

Immune-related Objective Response (irOR) is defined as irCR or irPR according to irRECIST from the first trial treatment administration until irPD or death due to any cause. Both irCR and irPR must be confirmed by repeat assessments performed no less than 4 weeks after the criteria for immune-related response are first met. Also, irPD must be confirmed by a second, consecutive assessment at least 4 weeks apart. Immune-related OR rate (irORR) is the proportion of subjects with irOR in the analysis set.

6.3.2 Treatment Beyond Radiographic Progression

Recognition of unconventional response events mainly overall tumor regression after the appearance of new lesions that previously were assessed as progressive disease by RECIST criteria led to the development of Immune-related RECIST (irRECIST) [89] and the Immune-modified RECIST (imRECIST) criteria [88]. Adoption of these disease criteria have been seen to allow a better assessment of the clinical efficacy of immunotherapy by capturing additional data from patients who experienced a tumor flare or delayed impact of the evolving immune response mostly in terms of improved DCR and PFS. In order for this approach to not negatively affect patient safety certain criteria must be fulfilled to safely allow treatment beyond conventionally assessed disease progression. Patients who are treated beyond RECIST defined progressive disease must be stable performance status without evidence of clinical deterioration or have any new physiology process that requires urgent additional therapy. Patients will have a follow-up restaging assessment after the completion of their next cycle of treatment (≥ 4 weeks) to confirm their disease has not progressed further and they can safely continue treatment.

Patient will be re-evaluated for response as outlined in the Study Calendar, **APPENDIX F**.

6.3.3 Disease Parameters for RECIST criteria

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

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

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

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

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

Target lesions: All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

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

6.3.4 Methods for Evaluation of Measurable Disease

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

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

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

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

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

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

protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

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

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

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

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.

b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

c. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

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

6.3.5 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

6.3.6 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

6.3.7 Evaluation of Best Overall Response

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

For Patients with Measurable Disease (i.e., Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks. from baseline**

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.
Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration."* Every effort should be made to document the objective progression even after discontinuation of treatment.

For Patients with Non-Measurable Disease (i.e., Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised

6.3.8 Duration of Reponses

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

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

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

6.3.9 Relapse Disease (after CR)/ Progressive Disease (after PR/SD)

Relapse Disease (after CR)/ Progressive Disease (after PR/SD) requires the following:

- Appearance of any new lesion more than 1.5 cm in any axis during or at the end of therapy, even if other lesions are decreasing in size. Increased FDG uptake in a previously unaffected site should only be considered relapsed or progressive disease after confirmation with other modalities. Thus, a therapeutic decision should not be made solely on the basis of the PET without histologic confirmation.

- At least a 20% increase from nadir in the SPD of any previously involved nodes, or in a single involved node, or the size of other lesions (e.g., splenic or hepatic nodules). To be considered progressive disease, a lymph node with a diameter of the short axis of less than 1.0 cm must increase by 50% and to a size of 1.5 x 1.5 cm or more than 1.5 cm in the long axis.
- At least a 50% increase in the longest diameter of any single previously identified node more than 1 cm in its short axis.

6.3.10 Time to Progression

Time to progression will be measured from the date of protocol consent until death of progressive disease is documented.

6.3.11 Progression-Free Survival

Progression-free survival (PFS) is defined as the duration of time from the date of study enrollment until time of disease relapse, disease progression, or death, whichever occurs first.

6.3.12 Overall Survival

Overall survival (OS) is defined as the time from the date of study enrollment until time of death from any cause.

6.3.13 Event-Free Survival

Event-free survival (EFS) is defined as the duration of time from the date of study enrollment until time of disease relapse, disease progression, alternative therapy for renal cell carcinoma given (such as radiation), or death, whichever occurs first

6.4 IMMUNE-RELATED RESPONSE CRITERIA (IRRECIST)

Modified immune-related response criteria (irRECIST) will also be employed in this study. This new classification is based on the recent learning from clinical studies with cancer immunotherapies that even if some new lesions appear at the beginning of a treatment or if the total tumor burden does not increase substantially, tumor regressions or stabilizations might still occur later. For this trial, the concepts of the irRECIST are combined with RECIST 1.1. Please refer to **APPENDIX E** for further details.

6.4.1 Immune-related BOR (irBOR)

The duration of Immune-related best overall response is measured from the time measurement criteria are met for irCR or irPR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started). irSD, not meeting criteria for irCR or irPR, in absence of irPD.

The duration of overall irCR is measured from the time measurement criteria are first met for irCR until the first date that progressive disease is objectively documented. Confirmation of assessment might be delayed up to 12 weeks to confirm PD to account for flare.

6.5 TOXICITY CRITERIA

The following adverse event management guidelines are intended to ensure the safety of each patient while on the study. The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site

(http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm).

7 NIH REPORTING REQUIREMENTS/DATA AND SAFETY MONITORING PLAN

7.1 DEFINITIONS

Please refer to definitions provided in Policy 801: Reporting Research Events found here.

7.2 OHSRP OFFICE OF COMPLIANCE AND TRAINING

7.2.1 Expedited Reporting

Please refer to the reporting requirements in Policy 801: Reporting Research Events and Policy 802 Non-Compliance Human Subjects Research found here. **Note:** Only IND Safety Reports that meet the definition of an unanticipated problem will need to be reported per these policies.

7.2.2 IRB Requirements for PI Reporting at Continuing Review

Please refer to the reporting requirements in Policy 801: Reporting Research Events found here.

7.2.3 NCI Clinical Director Reporting

Problems expeditiously reported to the OHSRP in iRIS will also be reported to the NCI Clinical Director. A separate submission is not necessary as reports in iRIS will be available to the Clinical Director.

In addition to those reports, all deaths that occur within 30 days after receiving a research intervention should be reported via email to the Clinical Director unless they are due to progressive disease.

To report these deaths, please send an email describing the circumstances of the death to Dr. Dahut at NCICCRQA@mail.nih.gov within one business day of learning of the death.

7.3 NIH REQUIRED DATA AND SAFETY MONITORING PLAN

7.3.1 Principal Investigator/Research Team

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

All data will be collected in a timely manner and reviewed by the principal investigator or a lead associate investigator. Events meeting requirements for expedited reporting as described in section **7.2.1** will be submitted within the appropriate timelines.

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

8 SPONSOR SAFETY REPORTING

8.1 DEFINITIONS

8.1.1 Adverse Event

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavorable and unintended sign (including

an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (ICH E6 (R2))

8.1.2 Serious Adverse Event (SAE)

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

- Death,
- A life-threatening adverse event (see section **8.1.3**)
- Inpatient hospitalization or prolongation of existing hospitalization
    - A hospitalization/admission that is pre-planned (i.e., elective or scheduled surgery arranged prior to the start of the study), a planned hospitalization for pre-existing condition, or a procedure required by the protocol, without a serious deterioration in health, is not considered a serious adverse event.
    - A hospitalization/admission that is solely driven by non-medical reasons (e.g., hospitalization for patient or subject convenience) is not considered a serious adverse event.
    - Emergency room visits or stays in observation units that do not result in admission to the hospital would not be considered a serious adverse event. The reason for seeking medical care should be evaluated for meeting one of the other serious criteria.
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect.
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

8.1.3 Life Threatening

An adverse event or suspected adverse reactions is considered “life-threatening” if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death. (21CFR312.32)

8.1.4 Severity

The severity of each Adverse Event will be assessed utilizing the CTCAE version 5.

8.1.5 Relationship to Study Procedure

All AEs will have their relationship to study product assessed using the terms: related or not related.

- Related – There is a reasonable possibility that the study product caused the adverse event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study product and the adverse event.

- Not Related – There is not a reasonable possibility that the administration of the study product caused the event.

8.2 ASSESSMENT OF SAFETY EVENTS

AE information collected will include event description, date of onset, assessment of severity and relationship to study product and alternate etiology (if not related to study product), date of resolution of the event, seriousness and outcome. The assessment of severity and relationship to the study product will be done only by those with the training and authority to make a diagnosis and listed on the Form FDA 1572 as the site principal investigator or sub-investigator. AEs occurring during the collection and reporting period will be documented appropriately regardless of relationship. AEs will be followed through resolution.

SAEs will be:

- Assessed for severity and relationship to study product and alternate etiology (if not related to study product) by a licensed study physician listed on the Form FDA 1572 as the site principal investigator or sub-investigator.
- Recorded on the appropriate SAE report form, the medical record and captured in the clinical database.
- Followed through resolution by a licensed study physician listed on the Form FDA 1572 as the site principal investigator or sub-investigator.

For timeframe of recording adverse events, please refer to section **6.1**. All serious adverse events recorded from the time of first investigational product administration must be reported to the sponsor.

8.3 REPORTING OF SERIOUS ADVERSE EVENTS

Any AE that meets protocol-defined serious criteria or meets the definition of Adverse Event of Special Interest that require expedited reporting must be submitted immediately (within 24 hours of awareness) to OSRO Safety using the CCR SAE report form. Any exceptions to the expedited reporting requirements are found in section **8.4**.

All SAE reporting must include the elements described in section **8.2**

SAE reports will be submitted to the Center for Cancer Research (CCR) at: OSROSafety@mail.nih.gov and to the CCR PI and study coordinator. CCR SAE report form and instructions can be found at: https://ccrod.cancer.gov/confluence/display/CCRCRO/Forms+and+Instructions

Following the assessment of the SAE by OSRO, other supporting documentation of the event may be requested by the OSRO Safety and should be provided as soon as possible.

8.4 WAIVER OF EXPEDITED REPORTING TO CCR

As death due to disease progression is part of the study objectives, and captured as an endpoint in this study, it will not be reported in expedited manner to the sponsor. However, if there is evidence suggesting a causal relationship between the study drug and the event, report the event in an expedited manner according to section **8.3**.

8.5 SAFETY REPORTING TO THE PHARMACEUTICAL COLLABORATORS

Reporting will be per the collaborative agreement.

8.5.1 CTEP

Copies of all IND Safety Reports submitted to the FDA should be forwarded electronically to CTEPSupportAE@tech-res.com (please provide protocol number in subject line).

8.6 REPORTING PREGNANCY

All required pregnancy reports/follow-up to OSRO will be submitted to: OSROSafety@mail.nih.gov and to the CCR PI and study coordinator. Forms and instructions can be found here: https://ccrod.cancer.gov/confluence/display/CCRCRO/Forms+and+Instructions

8.6.1 Maternal exposure

If a patient becomes pregnant during the course of the study, the study treatment should be discontinued immediately, and the pregnancy reported to the Sponsor no later than 24 hours of when the Investigator becomes aware of it. The Investigator should notify the Sponsor no later than 24 hours of when the outcome of the Pregnancy become known.

Pregnancy itself is not regarded as an SAE. However, congenital abnormalities or birth defects and spontaneous miscarriages that meet serious criteria (section **8.1.2**) should be reported as SAEs.

The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) should be followed up and documented.

8.6.2 Paternal exposure

Male patients should refrain from fathering a child or donating sperm during the study and for 30 days after the last dose of avelumab.

Pregnancy of the patient's partner is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) occurring from the date of the first dose until 30 after the last dose should, if possible, be followed up and documented.

8.7 REGULATORY REPORTING FOR STUDIES CONDUCTED UNDER CCR-SPONSORED IND

Following notification from the investigator, CCR, the IND sponsor, will report any suspected adverse reaction that is both serious and unexpected. CCR will report an AE as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the study product and the adverse event. CCR will notify FDA and all participating investigators (i.e., all investigators to whom the sponsor is providing drug under its INDs or under any investigator's IND) in an IND safety report of potential serious risks from clinical trials or any other source, as soon as possible, in accordance to 21 CFR Part 312.32.

All serious events will be reported to the FDA at least annually in a summary format.

9 CLINICAL MONITORING

As a sponsor for clinical trials, FDA regulations require the CCR to maintain a monitoring program. The CCR's program allows for confirmation of: study data, specifically data that could affect the interpretation of primary and secondary study endpoints; adherence to the protocol, regulations, ICH E6, and SOPs; and human subjects protection. This is done through independent verification of study data with source documentation focusing on:

- Informed consent process
- Eligibility confirmation
- Drug administration and accountability
- Adverse events monitoring
- Response assessment

The monitoring program also extends to multi-site research when the CCR is the coordinating center.

This trial will be monitored by personnel employed by a CCR contractor. Monitors are qualified by training and experience to monitor the progress of clinical trials. Personnel monitoring this study will not be affiliated in any way with the trial conduct.

10 STATISTICAL CONSIDERATIONS

10.1 STATISTICAL HYPOTHESES

10.1.1 Primary Endpoints

Overall Response (CR + PR) by irRECIST 1.1 criteria in patients who receive at least 1 cycle of therapy with the 4 mcg/kg dose of rhIL-15.

10.1.2 Secondary Endpoints

- Rate and severity of AEs, duration of response, progression-free survival and overall survival in patients who receive at least 1 cycle of therapy
- Changes in percentage and absolute number of peripheral blood lymphocyte subsets.
- Quantitation of ADCC performed *ex vivo* on PBMCs obtained from the patients before and during treatment.
- Characterization of changes in immune cell infiltrates of tumor deposits by immunohistochemical and molecular analysis of core biopsies obtained before and during treatment

10.2 SAMPLE SIZE DETERMINATION

The primary objective of this trial is to determine the efficacy of combination treatment of CIV rhIL-15 on days 1-5 and IV anti PDL-1 avelumab on day 8 and 22 of the 28-day cycle in patients with treatment refractory PD-L1+ ($\geq$ 5%) metastatic clear-cell renal carcinoma in terms of overall response. All patients must have failed or relapsed and have progressive disease after at least 2 prior therapies that include multityrosine kinase inhibitor like axitinib or sunitinib and an anti-PD1

or PD-L1 ICI therapy like nivolumab. The primary endpoint will be overall response (OR) per irRECIST 1.1 criteria.

A Simon two stage Simon Optimal Design will be used for the analysis of the primary endpoint of overall response rate. A minimum of 12 (3 in the 2mcg/kg safety run-in cohort (Cohort 1) and 9 evaluable in the first stage) and maximum of 25 patients will be enrolled in order to have 17 evaluable patients treated at the recommended phase 2 dose for the CIV rhIL-15 schedule at dose 4 mcg/kg/day. A maximum of 19 patients may be enrolled in the phase 2 part of this trial to compensate for inevaluable patients. The sample size for this trial is based on the plan for 3 to 6 patients treated in the 2 mcg/kg/day safety run-in cohort and to accurately assess target 25% response rate in the 4 mcg/kg dosing cohort with a power of 80% to determine the feasibility if this rate were true. The overall Type I error was set at 5% and power at 80% that assumes a null hypothesis success rate of 5% versus a treatment with a 25% response rate. Patients treated in the 2 mcg/kg/day safety cohort will not be included in the primary end point analysis but will be included in the safety cohort and be assessed for the secondary endpoints.

Stage 1 for the 4 mcg/kg dose level will consist of 9 evaluable patients to provide evidence of effectiveness and safety. If at least 1 of the 9 patients achieves a radiographic response (> 20% reduction in tumor volume) the study will be allowed to recruit the total sample size of 17 evaluable patients, otherwise it will be stopped for futility (Stage I boundary). The second stage of the design requires 3 or more of the 17 patients to have a positive response for the treatment to be considered worthy of further investigation. If the null hypothesis is true, there is a 63% chance of terminating after Stage I. If the probability of success is actually 0.25, there is a 92% chance that 1 or more patients will exhibit a 20% reduction in tumor volume at Stage I. Patients discontinued from the trial will not be replaced and counted in an "Intent to Treat" analysis as evaluable and treatment failures. At the end of the trial, we will report poor performance if the treatment is rejected at Stage I, not meeting the criteria of at least 1 success in 9 cases. If there is no success at Stage II (at most 2 responses in 17 patients), we will report a failure to reject the null hypothesis using the conditional probability of the added patients.

To ensure that this combination, which has not been administered to patients previously, and the dose levels chosen for CIV rhIL-15 are safe, 3 to 6 patients will be treated at the 2 mcg/kg/day dose level to confirm the absence of dose limiting toxicities. Once the safety of the 2 mcg/kg dose level is confirmed the first 3 or 6 patients treated at the intended phase II dose of 4 mcg/kg/day will be evaluated likewise for dose limiting toxicities. If unacceptable toxicity is observed in ≥ 2 of the first 3 or 6 patients treated at these dose levels, entry into the trial and all treatment will be halted to review the safety data to determine if the treatment plan should be altered or the study terminated. If DLT that halts the trial is not observed in these safety run-in cohorts, the trial will proceed to the efficacy assessment as specified above. The protocol will be amended to include information from the Safety Run-in cohorts prior to opening phase II.

10.2.1 Early stopping criteria

An early stopping criterion for toxicity for the whole trial itself would be if ≥ 2 of the first 9 or ≥ 4 of the first 17 patients has unacceptable toxicity or an irAE that required discontinuation of avelumab and/or initiation corticosteroid treatment.

10.3 POPULATION FOR ANALYSES

10.3.1 Evaluable for Toxicity

All patients will be evaluable for toxicity from the time of their first treatment with rhIL-15 and avelumab.

10.3.2 Evaluable for objective response

Only those patients who have measurable disease present at baseline and have received at least one cycle of therapy with 4mcg/kg dose of rhIL-15, will be assessed on an intent to treat basis. Patients who discontinue treatment or die and are not restaged will be considered to be non-responders and included in calculating the response rate. Patients will have their response classified according to the definitions stated above, Section **6.3**. (**NOTE:** Patients who exhibit objective disease progression prior to the end of Cycle 1 will also be considered evaluable).

10.3.3 Evaluable for Non-Target Disease Response

Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease and have received at least one cycle of therapy will be assessed on an intent to treat basis. Patients who discontinue treatment or die and are not restaged will be considered to be non-responders. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

10.4 STATISTICAL ANALYSES

10.4.1 General Approach

The response rate will be determined and reported along with a 95% confidence interval using the Agresti-Coull method [90]. Other time-to-event outcomes will be reported using Kaplan-Meier curves.

10.4.2 Analysis of Secondary Endpoints

Secondary clinical endpoints of the rate and severity of AEs will be summarized by grade and type of toxicity. The progression-free survival (PFS) and overall survival (OS) will be calculated from the on-study date using the Kaplan Meier method. For PFS and OS, censoring time is defined as time from baseline to date of last follow-up. Duration of response for responders also calculated using the Kaplan-Meier approach is defined as time from the initial response to progression or death, whichever occurs first. Censoring time for duration of response is defined as time from the initial response to date of last follow-up.

The secondary objectives include characterization of biological effects of this treatment and determination of effects of IL-15 on the ADCC capacity of ex vivo PBMCs. These exploratory analyses will be summarized.

11 COLLABORATIVE AGREEMENTS

11.1 COOPERATIVE RESEARCH AND DEVELOPMENT AGREEMENT (CRADA) - EMD SERONO

This study will be incorporated into an existing CRADA (#02666) between the National Cancer Institute and EMD Serono, the manufacturer of avelumab.

12 HUMAN SUBJECTS PROTECTIONS

12.1 RATIONALE FOR SUBJECT SELECTION

All subjects from both sexes and all racial/ethnic groups are eligible for this study if they meet the eligibility criteria outlined in the protocol and provide informed consent to protocol participation. Pregnant or nursing mothers are excluded because of the potential teratogenic effects of therapy.

There have been no studies of IL-15 in patients with HIV on or off ART. Two non-human primates with SIV who were not on ART and received rhIL-15 on Study 2078-10804 both died, while subsequent animals who received viral suppression were seemingly unaffected. rhIL-15 may therefore contribute to morbidity/mortality in patients with a detectable viral load. Since potential toxicity of IL-15 and avelumab may interfere with ART adherence and optimal viral suppression, patients with HIV may be exposed to additional toxicity for unknown potential benefit of IL-15 and should therefore be excluded from this study.

We expect men and women to be equally represented among the enrolled patients.

12.2 PARTICIPATION OF CHILDREN

Subjects under the age of 18 are excluded because ccRCC is rare in young patients, and the inclusion of an occasional younger patient will not provide generalizable information that would justify their inclusion on this study. Additionally, because no dosing or adverse event data are currently available on the use of rhIL-15 in combination with avelumab in patients <18 years of age, children are excluded from this study, but may be eligible for future pediatric trials.

12.3 RISK/BENEFIT ASSESSMENT

12.3.1 Known Potential Risks

The potential risks of adding rhIL-15 to avelumab include, in particular infusion reactions (including chills, fever, hypotension, headache, flushing, dizziness), fatigue, rash, Liver Function Test (LFT) abnormalities, and cytopenias.

Since fevers, rigors, lymphopenia, and LFT elevations occurred only during IL-15 infusion in the continuous IV trial, and since avelumab is not given concomitantly, these toxicities are not expected to overlap. Avelumab manufacturer recommendations for discontinuing therapy will be followed, including for grade 3-4 LFT elevations. Fatigue and rash are potential overlapping toxicities, and both will be monitored closely.

12.3.2 Risks related to Imaging

CT scans often use a contrast agent. There is a small risk of having a reaction to the contrast and most often include nausea, pain in the vein where the contrast is given, headache, metallic and/ or bitter taste in the mouth and a warm, flushing feeling. Rarely, some people have more severe allergic reactions to the contrast which may include skins rashes, shortness of breath, wheezing or low blood pressure.

12.3.3 Risks from Radiation Exposure

The procedures for performing the CT scans will follow clinical policies, no special procedures apply to these additional assessments for research purposes. In summary, subjects may receive additional radiation exposure from up to seven (7) additional CT scans of the neck, chest, abdomen, and pelvis.

The total additional radiation dose for research purposes will be approximately 9.1 rem.

12.3.4 Blood draws

Side effects of blood draws include pain and bruising, lightheadedness, and rarely, fainting.

12.3.5 MRI

People are at risk for injury from the MRI magnet if they have some kinds of metal in their body. People with fear of confined spaces may become anxious during an MRI. Those with back problems may have back pain or discomfort from lying in the scanner. The noise from the scanner is loud enough to damage hearing, especially in people who already have hearing loss.

There are no known long-term risks of MRI scans.

12.3.6 Gadolinium enhanced MRI

During part of the MRI patient may receive gadolinium, a contrast agent, through an intravenous (IV) catheter (small tube). It will be done for research purposes.

The risks of an IV catheter include bleeding, infection, or inflammation of the skin and vein with pain and swelling. Participants undergoing gadolinium enhanced MRIs may also be at risk for kidney damage.

Most of the gadolinium contrast is eliminated in the urine. However, recent studies have found very small amounts of residual gadolinium in the body, including the brain and bone, by imaging and at autopsy. Macrocyclic gadolinium-containing contrast agents are substantially less likely to leave gadolinium behind than linear agents. There is presently no evidence that the retained gadolinium is associated with any adverse effects or other health risks. Participants undergoing gadolinium enhanced MRIs may also be at risk for kidney damage.

12.3.7 Tumor Biopsy (Optional)

All care will be taken to minimize risks that may be incurred by tumor sampling. However, there are procedure-related risks (such as bleeding, infection, and injury) that will be explained fully during informed consent.

12.3.8 Electrocardiogram

Some skin irritation can occur where the ECG/EKG electrodes are placed. The test is completely painless, and generally takes less than a minute to perform.

12.3.9 Central line

A non-tunneled central catheter is a soft tube a doctor puts into a vein leading to your heart. It is a way to take blood samples or give you fluids, medicines, or nutrients over a long period of time. Possible side effects include pain, bleeding, bruising, and, on rare occasions, swelling in your arm, chest, neck, or face on the same side as the catheter or infection.

12.3.10 Known Potential Benefits

The potential benefit of adding rhIL-15 to avelumab in treatment of metastatic refractory ccRCC is unknown, but single-agent ICI have shown activity as outlined in Section **1.2.4**.

12.3.11 Assessment of Potential Risks and Benefits

An estimated 20 to 50 % of mRCC are PD-L1+ [34], and since the anti-PD-L1 antibody avelumab has shown ADCC activity *in vitro*, agents that may enhance ADCC by increasing number and activity of Fc-binding effector cells — such as rhIL15 — could improve efficacy of avelumab in these diseases. Although the clinical benefit of these drug(s) has not yet been established, the intent of offering this treatment is to provide a possible therapeutic benefit, and thus the patient will be carefully monitored for tumor response and symptom relief in addition to safety and tolerability. In addition to the tumor cells, PD-L1 is also expressed on normal immune cells. Since avelumab has potential for *in vivo* ADCC activity, immune cell subsets may change. However, when 123 different immune cell subsets were analyzed in 28 patients with solid tumors who received avelumab during a phase I trial, there were no changes at any of the time points in any of the 123 subsets tested regardless of their PD-L1 expression before and during treatment [43]. PBMC samples were obtained before Avelumab, and after 1, 3, and 9 doses of the drug. A limited number of immune cell subsets will also be tested in our trial, both in PBMCs and optional tissue biopsies.

12.4 Consent Process and Documentation

The informed consent document will be provided to the participant as applicable for review prior to consenting. A designated study investigator will carefully explain the procedures and tests involved in this study, and the associated risks, discomforts and benefits. In order to minimize potential coercion, as much time as is needed to review the document will be given, including an opportunity to discuss it with friends, family members and/or other advisors, and to ask questions of any designated study investigator. A signed informed consent document will be obtained prior to entry onto the study.

The initial consent process as well as re-consent, when required, may take place in person or remotely (e.g., via telephone or other NIH approved remote platforms used in compliance with policy, including HRPP Policy 303) per discretion of the designated study investigator and with the agreement of the participant. Whether in person or remote, the privacy of the subject will be maintained. Consenting investigators (and participant, when in person) will be located in a private area (e.g., clinic consult room). When consent is conducted remotely, the participant will be informed of the private nature of the discussion and will be encouraged to relocate to a more private setting if needed.

13 REGULATORY AND OPERATIONAL CONSIDERATIONS

13.1 Study Discontinuation and Closure

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to investigators, funding agencies, the Investigational New Drug (IND) sponsor and regulatory authorities, as applicable. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB and/or Food and Drug Administration (FDA).

13.2 QUALITY ASSURANCE AND QUALITY CONTROL

The clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion. An individualized quality management plan will be developed to describe a site's quality management.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

13.3 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the National Cancer Institute has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

13.4 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s). This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), and/or regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at the/each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the NCI CCR. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by the clinical site(s) and by NCI CCR research staff will be secured and password protected. At the end of the study, all study databases will be archived at the NIH.

To further protect the privacy of study participants, a Certificate of Confidentiality has been issued by the National Institutes of Health (NIH). This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. By protecting researchers and institutions from being compelled to disclose information that would identify research participants, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to participants.

14 PHARMACEUTICAL INFORMATION

14.1 RHIL-15 (NSC #745101) IND# 100820

14.1.1 Source/Acquisition and Accountability

rhIL-15 is an investigational agent supplied to investigators by the Cancer Therapy Evaluation Program (CTEP), Division of Cancer Treatment and Diagnosis (DCTD), NCI.

14.1.2 Drug Summary Information

14.1.2.1 Chemical Name or Amino Acid Sequence

The 115 amino acid coding sequence of the pET28b/IL-15 cistron is as follows:

MNWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDA
SIHDTVENLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS

14.1.2.2 Other Names

Recombinant Human Interleukin -15; Recombinant Human IL-15; rhIL-15

14.1.2.3 Classification

Recombinant human interleukin-15 (rhIL-15) is a cytokine of the 4-alpha helix bundle family of cytokines whose mature form consists of 115 amino acids. It has two cystine disulfide cross linkages at positions Cys 42-Cys 88 and Cys 35-Cys 85.

14.1.2.4 Molecular Weight (M.W.)

12,898.8 Daltons

14.1.2.5 Mode of Action

IL-15 interacts with a private receptor subunit IL- 15R alpha as well as the IL-2/IL-15R beta chain shared with IL-2 and the common gamma chain shared with IL-2, IL-4, IL-7, IL-9 and IL-21. IL-15 shares a number of biological activities with IL-2, including stimulation of the proliferation of activated CD4+, CD8+ as well as gamma-delta subsets of T cells. IL-15 also stimulates the proliferation of NK cells and acts as a co-stimulator with IL-12 to facilitate the production of Interferon-gamma and TNF-alpha.

14.1.3 How Supplied

IL-15 is manufactured by the Biopharmaceutical Development Program (BDP) and distributed by the Pharmaceutical Management Branch (PMB) ant CTEP. IL-15 is supplied as a sterile, frozen liquid product in single use vials containing no preservatives. Currently, IL-15 is supplied as 147 mcg / 0.3 mL (490 mcg/mL) in a 3 mL glass vial. The IL-15 is formulated in 25 mM sodium phosphate containing 0.5 M sodium chloride at a pH of 7.4.

NOTE: IL-15 vial content may vary between lots and protocols. Use caution and consult the protocol document for specific preparation instructions when preparing each dose.

14.1.4 Preparation

Vials of frozen IL-15 should be thawed at ambient room temperature and used within 5 hours of thawing. Upon thawing, the solution should be clear and colorless with no evidence of particulates or foreign matter. The infusion solutions should be mixed in a PVC bag.

14.1.5 Storage

IL-15 vials should be stored at or below (-70°C).

14.1.6 Stability

14.1.6.1 Vials

Stability studies of the intact vials are ongoing.

14.1.6.2 Prepared Infusion

The rhIL-15 infusion solution is stable at a concentration of 1 mcg/mL with 0.1% HSA for 4 hours at controlled room temperature (15°C–30°C) prior to initiation of the 24-hour infusion or 24 hours at 2-8°C prior to initiation of the 24-hour infusion. This stability information was previously documented by the Biopharmaceutical Development Program (BDP) of Leidos Biomedical Research, Inc., the drug manufacturer.

14.1.7 Administration

For all dose levels, the dose of rhIL-15 will be diluted in the appropriate volume of 0.1% human serum albumin (HSA) in 5% dextrose in water, USP (D5W) or in 0.9% sodium chloride (NS) to reach a final rhIL-15 concentration of 1 mcg/mL (see Dilution instruction, **APPENDIX C**). The rhIL-15 infusion will be administered to the patient by continuous intravenous infusion (civ) at a dose in mcg/kg/day

determined by the dose level at which the patient is enrolled. Each bag (total 5 bags over 5 days) will be infused over 24 hours using a portable ambulatory pump on the inpatient unit (cycle 1) or in the outpatient setting (cycles 2-4, if deemed appropriate by the PI) for a total of 120 hours. Bags must be changed every 24 hours. Treatment with rhIL-15 will begin within 4 hours of preparation of the infusion bag and the infusion must be completed within 24 hours from the time drug administration begins. Otherwise a new infusion bag must be prepared to complete administration of the remaining dose.

See **Table 7** for Drug Regimen, and Section **3.2.1** for supportive care measures.

14.1.8 Toxicity

The Comprehensive Adverse Event and Potential Risks List (CAEPRs) for Recombinant Human IL-15 provides a single list of reported and/or potential adverse events (AE) associated with the agent using a uniform presentation of events by body system. . In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. The CAEPR does not provide frequency data; refer to the Investigator's Brochure for this information. Below is the CAEPR for Recombinant Human IL-15.

Version 1.3, January 2, 2019*

Adverse Events with Possible Relationship to Recombinant Human IL-15 (CTCAE 5.0 Term)	**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
BLOOD AND LYMPHATIC SYSTEM DISORDERS	
Anemia	***Anemia (Gr 2)***
Bone marrow hypocellular	
CARDIAC DISORDERS	
Sinus tachycardia	***Sinus tachycardia (Gr 2)***
GASTROINTESTINAL DISORDERS	
Abdominal pain	
Diarrhea	
Nausea	***Nausea (Gr 2)***
Vomiting	***Vomiting (Gr 2)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	
Chills	***Chills (Gr 2)***
Edema limbs	
Fatigue	***Fatigue (Gr 2)***
Fever	***Fever (Gr 2)***
Injection site reaction	
INFECTIONS AND INFESTATIONS	
Sepsis	
INVESTIGATIONS	
Alanine aminotransferase increased	
Aspartate aminotransferase increased	

Adverse Events with Possible Relationship to Recombinant Human IL-15 (CTCAE 5.0 Term)	**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Blood bilirubin increased	
Creatinine increased	
Lymphocyte count decreased	***Lymphocyte count decreased (Gr 2)***
Lymphocyte count increased	
Neutrophil count decreased	
Platelet count decreased	
White blood cell decreased	
METABOLISM AND NUTRITION DISORDERS	
Hypoalbuminemia	
Hypophosphatemia	***Hypophosphatemia (Gr 2)***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	
Generalized muscle weakness	
NERVOUS SYSTEM DISORDERS	
Dizziness	
Headache	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	
Dyspnea	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	
Dry skin	
Erythema multiforme	***Erythema multiforme (Gr 2)***
Skin and subcutaneous tissue disorders - Other (rash)	
VASCULAR DISORDERS	
Capillary leak syndrome	
Hypertension	***Hypertension (Gr 2)***
Hypotension	***Hypotension (Gr 2)***

*This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail

Adverse events reported on Recombinant Human IL-15 trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that Recombinant Human IL-15 caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Febrile neutropenia

CARDIAC DISORDERS - Atrial fibrillation; Chest pain - cardiac; Palpitations; Pericardial effusion; Pericardial tamponade; Sinus bradycardia; Ventricular tachycardia

GASTROINTESTINAL DISORDERS - Ascites; Constipation; Duodenal hemorrhage; Gastritis; Gastrointestinal disorders - Other (increased appetite); Ileus; Mucositis oral; Pancreatitis

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Edema face; Infusion related reaction; Infusion site extravasation; Multi-organ failure; Pain

IMMUNE SYSTEM DISORDERS - Autoimmune disorder

INFECTIONS AND INFESTATIONS - Tooth infection; Upper respiratory infection; Urinary tract infection

INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Bruising

INVESTIGATIONS - Alkaline phosphatase increased; Cardiac troponin I increased; Electrocardiogram QT corrected interval prolonged; GGT increased; INR increased; Lipase increased; Serum amylase increased; Weight gain; Weight loss

METABOLISM AND NUTRITION DISORDERS - Anorexia; Dehydration; Hyperkalemia; Hypocalcemia; Hypokalemia

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Back pain; Bone pain; Muscle weakness upper limb; Myalgia; Pain in extremity

NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Tumor pain

NERVOUS SYSTEM DISORDERS - Dysgeusia; Peripheral sensory neuropathy; Presyncope; Vasovagal reaction

PSYCHIATRIC DISORDERS - Anxiety; Psychosis

REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Genital edema

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Adult respiratory distress syndrome; Bronchopulmonary hemorrhage; Cough; Hypoxia; Laryngeal inflammation; Pleural effusion; Pneumonitis; Pulmonary edema; Wheezing

SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Erythroderma; Palmar-plantar erythrodysesthesia syndrome; Pruritus; Rash acneiform; Skin and subcutaneous tissue disorders - Other (skin plaques)

VASCULAR DISORDERS - Hot flashes; Visceral arterial ischemia

Note: Recombinant Human IL-15 in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent

14.1.9 CTEP Information

14.1.9.1 Agent ordering and Agent Accountability

NCI-supplied agents may be requested by eligible participating Investigators (or their authorized designee). The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The eligible participating investigators must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), NCI Biosketch, Agent Shipment Form, and Financial Disclosure Form (FDF). If there are several participating investigators, CTEP-supplied investigational agents for the study should be ordered under the name of one lead participating investigator at that institution.

IL-15 may be ordered from PMB when a patient is being worked up for the study.

Submit agent requests through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" account status, a "current" password, and active person registration status. For questions about drug orders, transfers, returns, or accountability, call or email PMB any time. Refer to the PMB's website for specific policies and guidelines related to agent management.

14.1.9.1.1 Agent Inventory Records

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, dispensing and final disposition of all agents received from the PMB using the appropriate NCI Investigational Agent (Drug) Accountability Record (DARF) available on the CTEP forms page. Store and maintain separate NCI Investigational Agent Accountability Records

for each agent, strength, formulation and ordering investigator on this protocol.

14.1.9.2 Investigator Brochure Availability

The current versions of the IBs for the agents will be accessible to site investigators and research staff through the PMB OAOP application. Access to OAOP requires the establishment of a CTEP IAM account and the maintenance of an "active" account status, a "current" password and active person registration status. Questions about IB access may be directed to the PMB IB Coordinator via email.

14.1.9.3 Useful Links and Contacts

- CTEP Forms, Templates, Documents: http://ctep.cancer.gov/forms/
- NCI CTEP Person Registration: RCRHelpDesk@nih.gov
- PMB policies and guidelines: http://ctep.cancer.gov/branches/pmb/agent_management.htm
- PMB Online Agent Order Processing (OAOP) application: https://ctepcore.nci.nih.gov/OAOP
- CTEP Identity and Access Management (IAM) account: https://ctepcore.nci.nih.gov/iam/
- CTEP IAM account help: ctepreghelp@ctep.nci.nih.gov
- IB Coordinator: IBCoordinator@mail.nih.gov
- PMB email: PMBAfterHours@mail.nih.gov
- PMB phone and hours of service: (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET)

14.2 AVELUMAB IND#100820 (NSC #799232)

14.2.1 Source/Acquisition and Accountability

Investigational supplies of Avelumab will be supplied by EMD Serono for use in this clinical trial.

14.2.2 Toxicity

Please refer to the IB (version 10, May 2020) for detailed toxicity information. In brief, in clinical studies thus far, most observed adverse events were either in line with those expected in patients with advanced tumors or with similar class effects of mAb blocking the PD-1/PD-L1 axis. Infusion-related reactions including drug hypersensitivity reactions and immune-mediated adverse reactions (immune-related pneumonitis, immune-related colitis, immune-related hepatitis, immune-related endocrinopathies (thyroid disorders, adrenal insufficiency, new onset type I diabetes mellitus, pituitary disorders), immune-related nephritis and renal dysfunction and other immune-related AEs (myositis, myocarditis, Guillain-Barré syndrome, uveitis, pancreatitis and myasthenia gravis/myasthenic syndrome) have been identified as important risks for avelumab. Detailed guidelines for the management of immune-related adverse events and infusion-related reactions have been incorporated in this study protocol.

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform

presentation of events by body system. Frequency is provided based on 1738 patients. Below is the CAEPR for Avelumab.

Version 2.0, April 23, 2019

Adverse Events with Possible Relationship to Avelumab (CTCAE 5.0 Term) [n= 1738]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
	Anemia	
CARDIAC DISORDERS		
		Myocarditis[2]
		Pericarditis[2]
ENDOCRINE DISORDERS		
		Adrenal insufficiency[2]
		Hyperthyroidism[2]
		Hypophysitis[2]
		Hypopituitarism[2]
	Hypothyroidism[2]	
EYE DISORDERS		
		Uveitis[2]
GASTROINTESTINAL DISORDERS		
	Abdominal pain	
		Colitis[2]
	Diarrhea	
	Nausea	
	Pancreatitis[2]	
	Vomiting	

Adverse Events with Possible Relationship to Avelumab (CTCAE 5.0 Term) [n= 1738]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
	Chills	
Fatigue		
	Fever	
	Flu like symptoms[3]	
HEPATOBILIARY DISORDERS		
		Hepatic failure[2]
		Hepatobiliary disorders - Other (autoimmune hepatitis, immune-related hepatitis)[2]
IMMUNE SYSTEM DISORDERS		
		Autoimmune disorder[2]
		Cytokine release syndrome[3]
		Immune system disorders - Other (sarcoidosis)[2]
INFECTION AND INFESTATIONS		
	Infection[4]	
INJURY, POISONING AND PROCEDURAL COMPLICATIONS		
	Infusion related reaction[3]	
INVESTIGATIONS		
	Alanine aminotransferase increased	
	Alkaline phosphatase increased	

Adverse Events with Possible Relationship to Avelumab (CTCAE 5.0 Term) [n= 1738]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
	Aspartate aminotransferase increased	
	Blood bilirubin increased	
	CPK increased	
	Creatinine increased	
	GGT increased	
	Lipase increased	
	Lymphocyte count decreased	
	Neutrophil count decreased	
	Platelet count decreased	
	Serum amylase increased	
	Thyroid stimulating hormone increased	
METABOLISM AND NUTRITION DISORDERS		
	Anorexia	
		Hyperglycemia[2]
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
	Arthralgia[2]	
	Generalized muscle weakness	
	Muscle cramp	
	Myalgia[2]	
		Myositis[2]
	Pain in extremity	

Adverse Events with Possible Relationship to Avelumab (CTCAE 5.0 Term) [n= 1738]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
NERVOUS SYSTEM DISORDERS		
		Encephalopathy[2]
		Guillian-Barre syndrome[2]
		Myasthenia gravis[2]
		Nervous system disorders - Other (non-infectious encephalitis)[2]
		Nervous system disorders - Other (non-infectious meningitis)[2]
		Peripheral motor neuropathy
		Peripheral sensory neuropathy[2]
RENAL AND URINARY DISORDERS		
		Renal and urinary disorders - Other (immune related nephritis)[2]
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
	Cough	
		Pneumonitis[2]
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
	Eczema	
	Pruritus	
	Rash acneiform	
	Rash maculo-papular	

*This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting

PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Immune-mediated adverse reactions have been reported in patients receiving avelumab. Adverse events potentially related to avelumab may be manifestations of immune-mediated adverse events. In clinical trials, most immune-mediated adverse reactions were reversible and managed with interruptions of avelumab), administration of corticosteroids and supportive care.

[3]Infusion reactions, including high-grade hypersensitivity reactions, anaphylaxis, and cytokine release syndrome, which have been observed following administration of avelumab, may manifest as fever, chills, shakes, itching, rash, hypertension or hypotension, or difficulty breathing during and immediately after administration of avelumab.

[4]Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

Adverse events reported on avelumab trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that avelumab caused the adverse event:

CARDIAC DISORDERS - Palpitations; Sinus tachycardia

EYE DISORDERS - Blurred vision; Dry eye

GASTROINTESTINAL DISORDERS - Abdominal distension; Constipation; Dry mouth; Dyspepsia; Flatulence; Mucositis oral

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Edema limbs; Localized edema; Malaise; Non-cardiac chest pain; Pain

INVESTIGATIONS - Electrocardiogram QT corrected interval prolonged; Investigations - Other (c-reactive protein increased); Weight gain; Weight loss

METABOLISM AND NUTRITION DISORDERS - Dehydration; Hypoalbuminemia; Hypokalemia; Hypomagnesemia; Hyponatremia; Hypophosphatemia

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Back pain; Bone pain

NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (tumor flare); Tumor pain

NERVOUS SYSTEM DISORDERS - Dizziness; Dysesthesia; Dysgeusia; Headache; Tremor

RENAL AND URINARY DISORDERS - Proteinuria

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Dyspnea; Hypoxia

SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Dry skin; Hyperhidrosis

VASCULAR DISORDERS - Flushing; Hot flashes; Hypertension

Note: Avelumab in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

14.2.3 Formulation and Preparation

Avelumab drug product is a sterile, clear, and colorless concentrate for solution presented at concentration of 20 mg/mL in European Pharmacopeia (Ph. Eur.) and United States Pharmacopeia (USP) type I glass vials closed with a rubber stopper and sealed with an aluminum Flip Off® crimp seal closure.

Each single-use vial contains 200 mg of avelumab as a preservative-free acetate-buffered solution (pH 5.2) containing Mannitol, and Polysorbate 20 (Tween 20).

For avelumab drug product, only excipients that conform to the current Ph. Eur. and/or the current USP are used.

14.2.4 Stability and Storage

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

Avelumab drug product must be stored at 2°C to 8°C until use. Store diluted solution at room temperature up to 77°F (25°C) for no more than 4 hours from the time of dilution. *OR* Under refrigeration at 36°F to 46°F (2°C to 8°C) for no more than 24 hours from the time of dilution. If refrigerated, allow the diluted solution to come to room temperature prior to administration. The storage condition is based on data from ongoing long-term stability studies with avelumab. Avelumab drug product stored at room (23°C to 27°C) or higher temperatures for extended periods of time might be subject to degradation. Avelumab drug product must not be frozen. Rough shaking of the solution must be avoided.

14.2.5 Administration Procedures

For administration in clinical trials, avelumab drug product may be diluted with 0.9% saline solution (sodium chloride injection) supplied in 250 mL infusion bags, alternatively, a 0.45% saline solution can be used if needed. The chemical and physical in-use stability for the infusion solution of avelumab in 0.45% or 0.9% saline solution has been demonstrated for a total of 24 hours at room temperature. However, from a microbiological point of view, the diluted solution should be used immediately. If not used immediately, it can be considered that the diluted product is sufficiently stable from a microbiological perspective for up to 8 hours when stored at ambient room temperature or up to 24 hours at 2°C to 8°C. The in-use storage times and conditions prior to administration are the responsibility of the user.

Prior to the preparation of the dilution for final infusion, allow each vial to equilibrate to room temperature. Use a disposable syringe equipped with a needle of suitable size to remove a volume of sodium chloride solution to be replaced by avelumab from the infusion bag and discard the removed solution. Use a new disposable syringe equipped with a needle of suitable size to inject a volume of avelumab drug product identical to the discarded volume of sodium chloride solution into the infusion bag. Gently invert the mixture 10 times. Infusion bags must not be shaken, in order to avoid foaming or excessive shearing of the protein solution. The preparation must be carefully inspected as it should result in a homogeneous looking clear solution, free of visible particles.

14.2.6 Returns and Reconciliations

Unused investigational products will be destroyed per routine pharmacy procedure.

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16 APPENDICES

16.1 APPENDIX A: PERFORMANCE STATUS CRITERIA

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

16.2 APPENDIX B: ASSAY FOR ADCC

- Peripheral blood mononuclear cells (PBMCs) should be isolated by Ficoll-High-Paque Density Gradient Centrifugation.
- The viable cells should be viably frozen and stored in liquid nitrogen.
- The ADCC assay will be performed on the same occasion for all samples of a given patient.
- Vials of frozen cells will be thawed using standard procedures 18 hours before the assay in accordance with our experience with normal donors.
- 1.5 million of patient's PBMCs obtained before and on day 15 following IL-15 injection will be tested in aliquots as follows:
    - Tested alone
    - Tested with untreated PD-L1-expressing Raji cells and with PD-L1-expressing Raji cells coated with avelumab for 5 hours.
    - In addition, we may utilize an ATL cell line in addition to Raji cells. These cell populations will be stained with CD107, CD3, CD56 and CD94.

16.3 APPENDIX C: IL-15 DILUTION INSTRUCTIONS

All dose preparations will be performed in a laminar flow hood in compliance with all legal requirements and in accordance with guidelines of recognized organizations.

0.1% human serum albumin (HSA) in 5% dextrose in water, USP (D5W), or in 0.9% sodium chloride (NS) may be used for the dilutions listed below.

Please note: The dosing examples listed below are for the 147 mcg/0.3 mL in a 3mL vial size and dilution ONLY. The following dosing chart may be used as a reference, but doses should always be re-calculated at the time of preparation. In the future, different concentrations of IL-15 may be available and doses and dilutions will need to be recalculated.

Dose Level 1 (2 mcg/kg) and Dose Level 2 (4 mcg/kg)

To prepare an IL-15 dose for Dose Level 1 (2 mcg/kg):

1. Thaw vial(s) of IL-15, **147 mcg/0.3 mL (490 mcg/mL)** at room temperature.
2. Using a 27-gauge needle, slowly draw up the required dose in a 1 mL syringe. Doses should be rounded to the nearest 0.01 mL.
3. Add the calculated volume of diluted IL-15 to 0.1% HSA in D5W, or in NS, in a PVC or polyolefin bag.
4. Label the bag with a 4-hour beyond-use date. The infusion may be started within 4 hours at room temperature, or within 24 hours if bag was kept at 2-8°C. The infusion must be completed within 24 hours of initiation.

Administered dose = _____ kg (Patient's weight) X _____ mcg/kg (DL) = _____ **mcg**

Prepared dose = _____ mcg (Administered dose) + 10 mcg (Overfill dose) = _____ **mcg**

IL-15 volume = _____ mcg (Prepared dose) ÷ 490 mcg/mL (vial concentration) = _____ **mL**

Total infusion volume =

_____ mcg (Prepared dose) ÷ 1 mcg/mL (final infusion concentration) = _____ **mL**

Diluent volume =

_____ **mL (Total infusion volume) -** _____ **mL (IL-15 volume) =** _____ **mL**

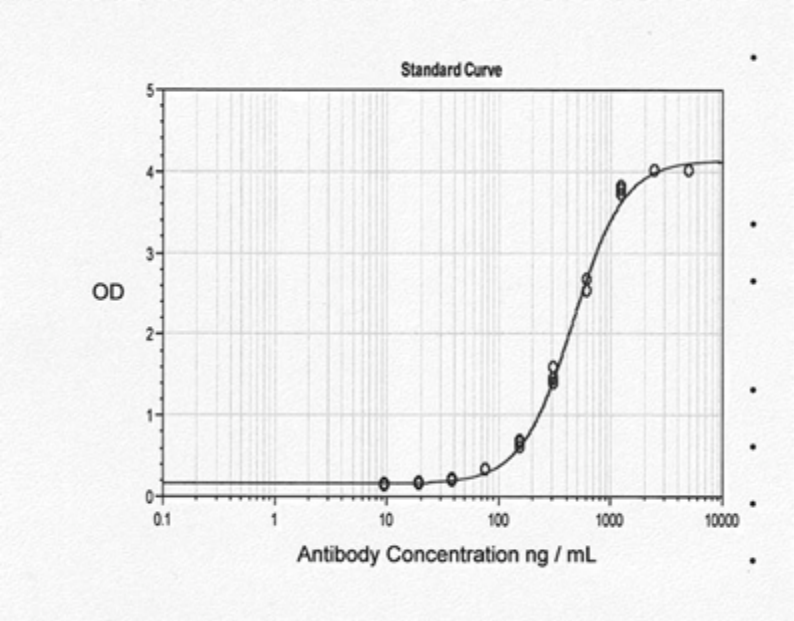
Patient's weight	IL-15 volume (490 mcg/ml)		Diluent volume		Total infusion volume (1 mcg/ml)	
	2mcg/kg	4 mcg/kg	2 mcg/kg	4 mcg/kg	2 mcg/kg	4 mcg/kg
60 kg	0.27	0.51	129.73	249.49	130 ml	250 ml
75 kg	0.33	0.63	159.67	309.37	160 ml	310 ml
90 kg	0.39	0.76	189.61	369.24	190 ml	370 ml
105 kg	0.45	0.88	219.55	429.12	220 ml	430ml

Dose calculation for obese patients:

For patients whose body mass index (BMI) is >30 kg/m2, the factor for body weight used in calculating IL-15 doses will be determined as follows:

Corrected body weight (kg) = 30 x (height [m])^2

16.4 APPENDIX D: ASSAY FOR ANTIBODIES TO RHIL-15



- Plates are coated with human IL-15 for 3 hours at 37°C, washed, blocked with 3% FBS and washed again.
- A standard curve for assay quantitation and quality control is constructed using serial dilutions of a commercial affinity purified goat anti-human IL-15 that is diluted in heat-inactivated normal human serum. The standard curve samples are incubated for 2 hours at 37°C and washed.
- Biotin conjugated IL-15 is added to each well, incubated 2 hours at 37°C, and the plates are washed.
- Alkaline phosphatase–conjugated streptavidin is added to each well for 2 hours at 37°C and then washed.
- The assay is developed with the addition of diethanolamine buffer with p-Nitrophenyl Phosphatase for 1 hour at 37°C and then immediately read at 405 nm.
- To detect antibodies to human IL-15 in test samples, serum from the test subject will be assayed in duplicate at dilutions of 1/3 and 1/9 concomitantly with the standard curve samples as above and the resultant OD obtained used to quantitate the level of antibody present.

16.5 APPENDIX E: MODIFIED IMMUNE-RELATED RESPONSE CRITERIA (IRRECIST)

This new classification is based on the recent learning from clinical studies with cancer immunotherapies that even if some new lesions appear at the beginning of a treatment or if the total tumor burden does not increase substantially, tumor regressions or stabilizations might still occur later. The irRC were created using bi-dimensional measurements (as previously widely used in the World Health Organization criteria). For this trial, the concepts of the irRC are combined with RECIST 1.1 to come up with the modified irRC.

For modified irRC, only target and measurable lesions are taken into account. In contrast to the RECIST 1.1 criteria, the modified irRC criteria (a) require confirmation of both progression and response by imaging at 6-8 weeks after initial imaging and (b) do not necessarily score the appearance of new lesions as progressive disease if the sum of lesion diameters of target lesions (minimum of 10 mm per lesion, maximum of 5 target lesions, maximum of 2 per organ) and measurable new lesions does not increase by ≥ 20%.

The same method of assessment and the same technique should be used to characterize each identified and reported target lesion(s) at baseline, during the trial, and at the end of trial visit. All measurements should be recorded in metric notation. The modified irRC based on RECIST 1.1 are displayed below.

Modified immune-related response criteria are defined as follows:

New measurable lesions: Incorporated into tumor burden.

New non-measurable lesions: Do not define progression but precludes (irCR).

Overall irCR:	Complete disappearance of all lesions (whether measurable or not) and no new lesions. All measurable lymph nodes also must have a reduction in short axis to 10 mm.
Overall irPR:	Sum of the longest diameters of target and new measurable lesions decreases ≥ 30%.
Overall irSD:	Sum of the longest diameters of target and new measurable lesions neither irCR, irPR, (compared to baseline) or irPD (compared to nadir).
Overall irPD:	Sum of the longest diameters of target and new measurable lesions increases ≥ 20% (compared to nadir), confirmed by a repeat, consecutive observations at least 4 weeks (normally it should be done at 6 weeks) from the date first documented.

16.6 APPENDIX F: STUDY CALENDAR

Procedure	**Screening**	**Baseline**	**Study Cycles**						**Disease Evaluations**	**End of Treatment and Disease Progression**	**Post-Treatment Follow-Up**		
			C1[1]			C2-4					Safety [2]	Follow-Up (Prior to PD)	Survival (Post-PD)
Scheduling Window (Days):	-28 to -1[3]		-14 [4]	8 (-3)	22 (-3)	1 (-3)	8 (-3)	22 (-3)	After C2 and C4 [5]	Treatment discon/PD [6]	Day 30 (+7)	Every 60 or 90 days [7]	Every 3 months [8]
Confirmation of Diagnosis [9]	X												
Physical Exam and ECOG PS [10]	X	X		X	X	X	X	X		X	X	X	
CBC with Differential	X	X	X	X	X	X	X	X		X	X	X	
Reticulocyte Count	X	X	X	X	X	X	X	X		X	X	X	
Chemistry Panels [11]	X	X	X	X	X	X	X	X		X	X	X	
LDH, Serum Lipase and Amylase	X	X	X	X	X	X	X	X		X	X	X	
PT/INR and aPTT	X	X	X			X				X	X	X	
Thyroid Function (i.e., TSH, T4)	X	X	X			X				X	X	X	
Urinalysis	X	X	X			X				X			
Pregnancy Test (urine/serum; WOCBP)	X	X	X										
Hepatitis B and C, HIV Antibody, HTLV-1/2	X												
Anti-nuclear antibody (ANA), rheumatoid factor (RF) and anti-thyroid antibody	X	X											
IL-2R		X	X			X							
Creatine phosphokinase (CPK), troponin	X	X	X							X		X	
Pulmonary function tests (PFTs) and TTE[12]	X												
T, B, NK cell subsets		X		X		X	X			X	X	X	
Imaging studies [13]	X	X							X	X		X	
MRI Lumbar Puncture [14]		X							X	X		X	

Procedure	**Screening**	**Baseline**	**Study Cycles**						**Disease Evaluations**	**End of Treatment and Disease Progression**	**Post-Treatment Follow-Up**		
			C1[1]			C2-4					Safety [2]	Follow-Up (Prior to PD)	Survival (Post-PD)
Scheduling Window (Days):	-28 to -1[3]		-14 [4]	8 (-3)	22 (-3)	1 (-3)	8 (-3)	22 (-3)	After C2 and C4 [5]	Treatment discon/PD [6]	Day 30 (+7)	Every 60 or 90 days [7]	Every 3 months [8]
Flow Cytometry[15]		X		X	X		X	X	X	X	X	X	
Clinical photography[16]		X							X	X		X	
Radiologic Evaluation/ tumor measurement[17]		X							X	X		X	
EKG	X												
Symptoms/Adverse Events Assessment, Concomitant Medication Review	X	X				X				X	X	X	
Research Blood/Tissue Samples [18]		X	Refer to Table Section **5.1**										
Survival Status													X

[1] On Day 8 and Day 22 of Cycle 1, vital signs ([VS] blood pressure, pulse, respiratory rate, temperature, oxygen saturation) will be assessed predose of avelumab (within 15 minutes of injection and/or infusion), and then every 15 minutes from the start of avelumab infusion for at least 2 hours. If vital signs are not stable after 2 hours, then continue monitoring every 15 minutes until stable on 2 consecutive repeated measurements.
[2] 30 days (+7) following last dose, and 90 days (+14) after last dose of avelumab (via clinic or phone/email). If initiating new anti-cancer therapy within 30 days after last dose of avelumab, 30-day safety follow-up visit must occur before first dose of new therapy.
[3] Screening and Baseline evaluations should be performed within 28 days prior to enrollment and dosing, respectively, unless otherwise noted and with the following exceptions: Confirmation of diagnosis (no time limit); HIV antibody, Hepatitis B surface antigen and Hepatitis C antibody and EKG (all within 3 months) **NOTE:** Any screening tests performed within the specified time frame for baseline do not need to be repeated.
[4] Within 14 days prior to dosing on C1D1, with the following exceptions: Pregnancy test (within 7 days of dosing; must be negative).
[5] ± 2 days. Confirmatory scans should also be obtained 4 weeks following initial documentation of objective response.
[6] To be done at end of treatment (30 days after last dose of study treatment; may be combined with 30 day safety follow-up, if timing coincides). If subject to initiate new anti-cancer therapy assessments should occur before the first dose of the new therapy.
[7] Follow-up to occur about every 60 days (±7 days) for first 6 months, every 90 days (±14 days) for 2 years; then every six months (± 28 days) for the duration of the study until disease progression or initiation of new anti-cancer therapy.

[8] After disease progression or initiation of new anti-cancer therapy, contact for survival about every 3 months (±4 weeks) for the duration of the study after stopping treatment.
[9] Pathologic review/confirmation of diagnosis by Laboratory of Pathology, NCI (no time limit) and PD-L1 as outlined in Section **5.2.4.1**. If archival sample is not available, a fresh punch or core biopsy of an appropriate easily accessible tumor deposit will be obtained.
[10] Physical exams to include medical history (i.e., complete at Screening/Baseline; interim on study and in follow-up), vitals, weight, and height (screening only).
[11] Chemistry panels include: Acute care, Hepatic, and Mineral.
[12] Diffusing capacity/alveolar volume (DLCO/VA), forced expiratory volume in 1 second (FEV1) for patients with significant pulmonary or smoking history or suspected tumor related pulmonary dysfunction and Transthoracic Echocardiograph for patients with suspected cardiac dysfunction that would increase their risk in receiving protocol treatment.
[13] Patients should have an evaluation of known sites of disease (CT, MRI, and in certain cases FDG-PET to better evaluate lesions of uncertain etiology) as part of the screening and baseline evaluations. Other body areas may be imaged if clinically indicated. MRI of the brain is only required in patients with suspected involvement of CNS.
[14] Patients with neurological symptoms or signs should undergo MRI scan of the brain and lumbar puncture
[15] Flow cytometry to be performed at baseline, and on Day 8 and 22 of each cycle, see Section **5.2.3**.
[16] To be performed in selected patients with skin lesions (as determined by PI or AI).
[17] Radiologic documentation must be provided for patients removed from study for progressive disease
[18] Samples for correlative research are to be collected as indicated in Section **5**