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A Phase 1 Study of Interleukin-15 in Combination with Avelumab (Bavencio) in Relapsed/Refractory Mature T-cell Malignancies

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Investigational Agents:

Drug Name:	Avelumab (MSB0010718C; NSC #799232)	Recombinant human IL-15 (rhIL-15; NSC #745101)
IND Number:	140549	
Sponsor:	Center for Cancer Research, NCI	
Manufacturer:	EMD Serono, Inc. (Company Study/Tracking #: MS100070_0039)	Biopharmaceutical Development Program (BDP)/Leidos Biomedical Research, Inc. under contract with DCTD, NCI
Supplier:	EMD Serono, Inc.	DCTD

Commercial Agents: None

PRÉCIS

Background:

- Mature T-cell cancers are a phenotypically heterogeneous group of malignancies which constitute 10-15% of all non-Hodgkin lymphomas (NHL). Patients with relapsed/refractory T cell lymphomas have limited therapeutic options, making new therapeutic approaches extremely important.
- 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.
- A significant number of T-cell malignancies express PD-L1, 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.

Objectives:

- To determine the safety and toxicity profile and the maximum tolerated dose (MTD) of continuous intravenous infusion (civ) rhIL-15 administration in combination with standard intravenous (IV) avelumab treatment

Eligibility:

- Age ≥ 18 years of age
- ECOG performance status of ≤ 1
- Histologically or cytologically confirmed relapsed and/or refractory T-cell lymphoma other than adult T-cell leukemia/lymphoma (ATLL), angioimmunoblastic T-cell lymphoma (AITL), peripheral T-cell lymphoma T follicular helper phenotype (PTCL-TFH), and enteropathy-associated T-cell lymphoma (EATL).
- Adequate organ and marrow function

Design:

- Open-label, single-center, non-randomized Phase 1 study
- Standard "3 + 3" design will be used to determine the MTD of dose-escalated rhIL-15 with fixed dose avelumab with a small expansion cohort at the MTD
- Maximum 6 cycles (28-day cycle) of combination therapy

- To explore all dose levels, including further evaluation in a dose expansion cohort, the accrual ceiling will be set at 30 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 safety and toxicity profile and the maximum tolerated dose (MTD) of continuous intravenous infusion (civ) rhIL-15 administration in combination with standard intravenous (IV) avelumab treatment

1.1.2 Secondary Objective

- Evaluate the potential antitumor activity of combination rhIL-15 and avelumab
- Assess PD-L1, PD-L2 and PD-1 expression before and after treatment with rhIL-15 and avelumab, and correlate expression with treatment response
- 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)

1.2 BACKGROUND AND RATIONALE

1.2.1 Mature T-cell malignancies

Mature T-cell cancers are a phenotypically heterogeneous group of malignancies which constitute 10-15% of all non-Hodgkin lymphomas (NHL)(1). Excluding a small proportion of indolent subtypes, they are treatment-resistant and are associated with poor prognosis(2). The most common mature T-cell malignancies in the United States are: peripheral T-cell lymphoma (PTCL, including the angioimmunoblastic variant and anaplastic large cell lymphoma - ALCL), cutaneous T-cell lymphoma (CTCL), and adult T-cell leukemia/lymphoma (ATLL), with incidence ranging from 0.09/100,000 for ATLL to 1/100,000 for PTCL(3-6).

1.2.2 Treatment of relapsed/refractory PTCL

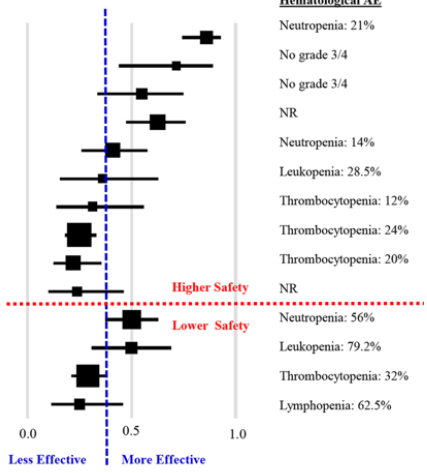
Three agents, pralatrexate, belinostat and romidepsin have received accelerated FDA approval for treatment of relapsed or refractory PTCL based on overall response rate (ORR) shown in Phase 2, single-arm studies. Pralatrexate is an antifolate investigated in 115 patients, 109 of whom were evaluable. ORR was 29% (95% CI, 21-39%), with 12 complete responses (CRs - 11%) and 20 partial responses (PRs- 18%)(7). Median duration of response was 10.1 months (range 1-673 days), median progression free survival (PFS) was 3.5 months, and median overall survival (OS) was 14.5 months. Seventy-four percent of patients had a grade 3 or 4 adverse event, most of which were hematological (19% grade 4 thrombocytopenia, 16% grade 3 anemia, 14% grade 3 thrombocytopenia and neutropenia).

Belinostat is a histone deacetylase inhibitor (HDACi) studied in 129 patients, 120 of whom were evaluable. ORR was 26%, with 12 CRs (10%) and 19 PRs (16%)(8). Median duration of response was 8.4 months (range NR-36 months). Median PFS was 1.6 months, and median OS was 7.9 months. Sixty-one percent of patients had a grade 3 or 4 adverse event. 22 patients died during treatment, of which 10 deaths (7.8%) were due to treatment-emergent adverse events arising within 30 days of the last belinostat dose. Romedepsin is another HDACi studied in 130 patients with PTCL. ORR was 25% including 15% CRs (19 of 130). Median PFS was 4 months(9).

A meta-analysis of available treatments for relapsed/refractory PTCL showed that, even though approved, belinostat and pralatrexate were less effective and less safe than several other regimens (**Figure 1**). Most effective of these regimens was the anti-CD30 immunotoxin brentuximab vedotin in anaplastic large cell lymphoma (ORR 86%), although, when given to unselected patients with PTCL-NOS, the ORR was significantly lower (ORR 41%)(6).

Figure 1: **Safety and efficacy of treatments for relapsed/refractory PTCL(6)**

Study	Drug regimens	Study Design	N	Median age	Major PTCL subtype	Median no. of prior therapy	ORR	Most frequent Grade 3/4 Hematological AE
Pro et al. (2012)	Brentuximab vedotin	Phase II trial	58	52	ALCL	2	86%	Neutropenia: 21%
Zinzani et al. (2000)	Gemcitabine	Prospective study	14	58	PTCL-NOS	3	72%	No grade 3/4
Zinzani et al. (2010)	Gemcitabine	Prospective study	20	54	PTCL-NOS	3	55%	No grade 3/4
Zelenetz et al. (2003)	ICE	Prospective study	43	46	PTCL-NOS	NR	63%	NR
Horwitz et al. (2014)	Brentuximab vedotin	Phase II trial	35	64	PTCL-NOS	2	41%	Neutropenia: 14%
Enblad et al. (2004)	Alemtuzumab	Phase II trial	14	61	PTCL-NOS	2	36%	Leukopenia: 28.5%
Huang et al. (2002)	13-cRA+interferon-α	Phase II trial	17	47	PTCL-NOS	1	31%	Thrombocytopenia: 12%
Coiffier et al. (2012)	Romidepsin	Phase II trial	130	61	PTCL-NOS	2	25%	Thrombocytopenia: 24%
Morschhauser et al. (2013)	Lenalidomide	Phase II trial	51	65	AITL	3	22%	Thrombocytopenia: 20%
d'Amore et al. (2010)	Zanolimumab	Phase II trial	21	69	AITL	2	24%	NR
Damaj et al. (2013)	Bendamustine	Phase II trial	58	66	AITL	1	50%	Neutropenia: 56%
Seok et al. (2012)	A-DHAP	Phase II trial	24	49	PTCL-NOS	NR	50%	Leukopenia: 79.2%
O'Connor et al. (2011)	Pralatrexate	Phase II trial	109	58	PTCL-NOS	3	29%	Thrombocytopenia: 32%
Foss et al. (2015)	Belinostat	Phase II trial	24	64	PTCL-NOS	NR	25%	Lymphopenia: 62.5%



1.2.3 Treatment of relapsed/refractory CTCL

There are five FDA-approved drugs for relapsed/refractory CTCL: bexarotene, romidepsin, vorinostat, mogamulizumab and brentuximab vedotin (for CD30-positive disease).

Bexarotene, a retinoid receptor X (RXR)-selective retinoid agonist, was given at two different dose levels to 94 patients with stage ≥IIB CTCL, of whom 31% had erythroderma and 10% had visceral

involvement(10). Only 16% of patients had ≥15% circulating Sézary cells, though 27% had detectable Sézary cells . ORR was 45-55%, with 1-5 CRs. One of five patients with circulating Sézary cells had a substantial decrease in counts. Six of 19 patients (32%) with generalized erythroderma, and four of 17 (24%) with Sézary Syndrome (SS) had a response. The most common grade 3 or 4 AEs were hyperlipidemia (34-45%) and pruritus (8-14%). One of 17 deaths were judged to be possibly drug related, that of a patient who developed liver failure with coagulopathy.

The HDAC inhibitor vorinostat was investigated in a phase IIB multicenter trial of 74 patients, 61 with advanced (stage ≥IIB) disease, including 30 with SS. ORR was 29.7% (1 CR, 21 PRs), including 10/30 patients with SS(11). Grade 3 or 4 AEs were seen in 28% of the patients, with the most common being fatigue (5%), pulmonary embolism (5%), thrombocytopenia (5%), and nausea (4%). Another HDAC inhibitor, romidepsin, was investigated in two concurrent Phase 2 trials with a combined total of 167 patients, 130 of whom with stage ≥IIB disease(12, 13). ORR was 34-38%, and a total of 10 patients (6%) had CRs, three of whom had SS. Reports of grade 3 or 4 AEs varied between the studies, with lymphopenia ranging from 21% to <10%, neutropenia 14% to <10%, and thrombocytopenia 6% to none. There were 10 deaths which occurred within 30 days of receiving the last dose of the drug, two from sepsis, one from hypertrophic cardiac disease, and the rest from disease progression.

Mogamulizumab is an anti-CCR4 antibody recently approved by the U.S. FDA, based on an open-label phase III study of 372 patients, with vorinostat as the control arm. ORR assessed by independent reviewers was 23% for mogamulizumab and 4% for vorinostat. Median PFS was 6.7 months in the mogamulizumab group versus 3.8 months in patients receiving vorinostat. The most common treatment-emergent AEs in the mogamulizumab group were infusion-related reactions, drug rash, diarrhea, and fatigue(14).

Chemotherapy, including CHOP-based regimens, have the highest response rates (50-88%), but duration of response is <6 months and high toxicity is associated with the treatment. More recently, a Phase 3 trial comparing brentuximab vedotin to methotrexate or bexarotene in $CD30^+$ CTCL, reported improvement in proportion of patients achieving an objective global response lasting at least 4 months (ORR4) at a median follow-up of 22.9 months, which was 56.3% with brentuximab vedotin vs. 12.5% with methotrexate or bexarotene(15).

1.2.4 Treatment of relapsed/ refractory anaplastic large cell lymphoma (ALCL)

Brentuximab vedotin is the only drug approved by the FDA for the treatment of CD30+ systemic ALCL relapsed after or refractory to chemotherapy. In a Phase 2 trial of 58 patients, 57% achieved CR and 29% achieved PR, with a median time to response of 5.9 weeks (which was the time of the first CT)(16). Median response duration was 12.6 months overall, and 13.2 months for patients who achieved CR.

1.2.5 Immune checkpoint inhibitors in T-cell malignancies

A Phase 1b trial of nivolumab in patients with relapsed and refractory hematologic malignancy involved 15 patients with CTCL (2 with mycosis fungoides and 2 with SS), 5 patients with PTCL and 3 with other forms of T-cell lymphoma(17). PD-L1 testing by immunohistochemistry (IHC) and molecular analysis was not done on all patients, and expression was not required for eligibility. There were no differences in AE frequency or severity between the B-cell and T-cell groups. Four patients (2 with CTCL and 2 with PTCL) had a PR, making the ORR 17%. Three of them had an ongoing response after 24.3, 50, and 78.6 weeks of follow-up, while one of the patients with PTCL

progressed after 10.6 weeks. Ten patients had stable disease (SD; median duration of 11 weeks), and the remaining 9 progressed during treatment.

The anti-PD-1 antibody pembrolizumab was given to 24 patients with MF/SS in a CITN multicenter Phase 2 study(18). The majority of patients had stage IIB or higher disease, and 15 had stage IVA SS. ORR was 38% (1 CR, 8 PR), with six patients having ≥90% improvement in skin disease as measured by the modified Severity Weighted Assessment Tool (mSWAT). Median TTR was 11 weeks, and 8 of 9 responses were ongoing at the time of the report. Notably, there was no association between response and skin tissue expression of PD-1, PD-L1, PD-L2, or infiltrating CD8+ T cells. A "skin flare" was reported in 40% of patients with SS. Two treatment-related SAEs were grade 2 pneumonitis and grade 3 diarrhea secondary to steroid-refractory duodenitis.

There is preclinical and clinical evidence to suggest that immune checkpoint inhibition may precipitate rapid progression in some forms of T-cell lymphoma, most notably those that are PD-1 (but not PD-L1) positive. In a phase II trial of nivolumab in patients with PTCL, ORR was 33%, with two CRs and two PRs among the 12 patients treated.(19) However, one of six patients with AITL progressed after the first dose, and three more experienced significant progression after the second or third dose of nivolumab. Notably, AITL tumor cells were shown to have high levels of PD-1(20), which may act as a tumor suppressor in T-cell lymphomagenesis.(21) PTCL with T follicular helper phenotype (PTCL-TFH) is another form of PTCL in which tumor cells are PD-1 positive, as is ATLL. A trial of single-agent nivolumab for ATLL (NCT02631746) was suspended for interim analysis when the first 3 patients enrolled developed accelerated disease progression within the first two doses of the drug.(22)

There are several ongoing Phase 2 trials that have yet to report results: nivolumab for relapsed/refractory PTCL (NCT03075553), pembrolizumab after auto-SCT for any HL, DLBCL, and T-NHL (NCT02362997); pembrolizumab for CTCL in combination with romidepsin (NCT03278782), radiation therapy (NCT03385226), and decitabine and pralatrexate (NCT03240211, which also includes patients with PTCL); atezolizumab for relapsed/refractory CTCL (NCT03357224); and avelumab for relapsed/refractory PTCL (NCT03046953).

1.2.6 Recombinant human IL-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 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 (CD215)(23-27). 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. 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 participates less in the capillary leak syndrome. Several studies in murine models highlighted the potential value of IL-15 therapy for neoplasia. The safety of IL-15 was evaluated in rhesus macaques. A 12-day bolus intravenous administration of 20 μg/kg/day of IL-15 to rhesus macaques was associated with a 4 to 8-fold increase in the number of circulating NK cells. When administered by continuous intravenous infusion (civ) at 20 μg/kg/day for 10 days, a 10-fold increase in the number of circulating NK cells, a 15-fold increase in the number of circulating monocytes and a massive 80 to 100-fold increase in the number of circulating effector memory CD8 T-cells was observed. Subcutaneous infusions at 20 μg/day for 10 days led to a 10-

fold expansion in the number of circulating effector memory CD8 T-cells. On the basis of 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.

1.2.7 Clinical trials using IL-15 monotherapy in the treatment of cancer

We initiated, executed and reported a first in-human Phase I study (NCT01021059) of bolus administered intravenous rhIL-15 in adults with refractory metastatic malignant melanoma and metastatic renal cell cancer(23) . This study was initially planned as a Phase 1 dose-escalation trial starting with an initial dose of 3 mcg/kg/day for 12 days. However, after the initial patient developed grade 3 hypotension, and another patient of the 5 patients at dose level 3 mcg/kg/day developed grade 3 thrombocytopenia, the protocol was amended to add the two lower doses of 1.0 and 0.3 mcg/kg/day. Two of four patients given 1.0 mcg/kg/day dose developed persistent grade 3 alanine aminotransferase (ALT) and aspartate aminotransferase (AST) elevations that were dose limiting. All 9 patients with IL-15 at 0.3 mcg/kg/day received 12 doses without a DLT, and the 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, and a drop in blood pressure 5 to 9 hours after the infusion to a nadir approximately 20 mm/Hg below pretreatment levels. These changes were concurrent with a maximum of 50-fold elevations of circulating IL-6 and IFn-γ concentrations.

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, followed by an influx and hyperproliferation yielding a 10-fold expansion in the number of NK cells that ultimately returned to baseline. There was a modest effect on the number of CD8+ T-cells but by day 8 of the infusion virtually all CD8+ T-cells expressed high levels of Ki67, CD38 and HLA-DR. In this first-in-human Phase 1 trial there were no responses, with stable disease as the best response. However, 5 patients manifested a decrease of between 10% and 30% of their marker lesions and 2 had clearing of lung lesions.

1.2.8 Clinical trials involving IL-15 administered by alternate dosing strategies

Ultimately, we concluded that it proved too difficult to administer IL-15 as an intravenous bolus infusion because of clinical toxicities produced by intense cytokine secretion that occurred within the first 2 hours after treatment. There were exceedingly high IL-15 C_{max} levels initially after bolus infusions that were sufficient to signal through the IL-2/IL-15R beta and γc receptor pair that IL-15 shares with IL-2, thereby contributing to the toxicities observed. To reduce the C_{max} and toxicity and to increase the period of time when IL-15 is at an optimal concentration for high-affinity IL-15 receptors we evaluated alternative dosing strategies, first in rhesus macaques. By administering IL-15 by civ or subcutaneously to these nonhuman primates the exceedingly high C_{max} observed by bolus infusion was avoided. In particular, with bolus intravenous infusions to rhesus macaques at 20 mcg/kg/day, the C_{max} was 720 pg/mL, in contrast with subcutaneous infusion of 20 mcg/kg/day the C_{max} was 50 pg/mL and with continuous infusion at 20 µg/kg/d the IL-15 C_{max} was between 2 and 4 pg/mL throughout the 10-day study period.

1.2.8.1 A Phase I Study of Subcutaneous Recombinant Human IL-15 (rhIL-15) in Adults with Metastatic Cancer (NCT01727076)

To translate this observation in collaboration with the Cancer Immunotherapy Trials Network

(CITN), we completed a Phase I trial of subcutaneous recombinant human IL-15 in cycles consisting of 5 daily injections of rhIL-15 given Monday-Friday for 2 weeks, then 2 weeks of observation with potential for additional cycles. Three patients each were enrolled in 0.25, 0.5, 1.0, and 2.0 mcg/kg/day dose levels and six patients were evaluated at 3.0 mcg/kg/day. Eighteen patients completed at least one cycle with one DLT at 3.0 mcg/kg/day and one serious adverse event, pancreatitis, at 2.0 mcg/kg/day. Flow-cytometry data indicated a consistent increase in the frequency of CD56bright CD3- negative NK cells peaking at day 15 (day 12 = last dose). The mean fold increase with 3 mcg/kg/day of IL-15 in circulating NK cell numbers peaked at 10.8-fold. The maximum fold increase in circulating CD8 + T cells was 3.3-fold. It was concluded that subcutaneous IL-15 was well tolerated and that the 3 mcg/kg/day dose level was safe for outpatient use.

1.2.8.2 Protocol ID Number: NCI-12-C-0113 A Phase I Study of a Continuous Intravenous Infusion of Recombinant Human Interleukin IL-15 (rhIL-15) in Adults with Metastatic Cancers (NCT01572493)

In a parallel clinical trial that we performed in the Clinical Center NIH, rhIL-15 was administered at progressively increasing doses (0.25, 0.5, 1.0, 2.0 and 4.0 mcg/kg/day) to groups of 3 patients each, with metastatic malignancy by civ for 10 days. Two dose-limiting toxicities were observed at 4.0 mcg/kg/day, hepatotoxicity and visceral arterial ischemia. Therefore, an expansion group study of 9 patients at the MTD of 2.0 mcg/kg/day was completed. This 2.0 mcg/kg/day dose level was well tolerated. None of the patients had an immune response to the IL-15. The pharmacokinetic pattern when IL-15 was administered by civ was quite distinct from that observed with bolus infusion. With bolus infusions of 3 mcg/kg/day the arithmetic mean C_{max} of 30,420 pg/mL was observed at the onset of the IL-15 administration, followed by a rapid decline in serum IL-15 levels. When IL-15 was administered by subcutaneous infusion the C_{max} at 4 hours after the subcutaneous administration of 3.0 mcg/kg/day was 6,480 pg/mL. With continuous intravenous infusion, there was a progressive increase of serum IL-15 levels with a C_{max} at 12 to 48 hours of 1,510 pg/mL, markedly lower than that observed with bolus infusions. The lower C_{max} observed with subcutaneous and civ was paralleled inversely by a 10-fold greater MTD at these levels compared to that with the bolus infusion. In the civ trial following the C_{max} at 12 to 48 hours there was a gradual decline to 8% of the maximum level by days 8-10 despite the fact that the IL-15 infusions were continued. We hypothesized that a factor for this decline in serum IL-15 concentration was the IL-15-induced increase in the number of IL-15 receptor bearing cells as well as the number of receptors (especially IL-2/IL-15Rβ [CD122] receptors) per cell that acted as a sink, binding some of the IL-15 administered.

The time course of the increase in host lymphoid cells showed an interesting pattern with civ. Within 1 to 3 days of the infusion initiation there was a rapid decline in the number of circulating NK cells, followed by a gradual increase until the termination of infusions. Of interest, during the 1 to 3 days immediately following termination of the infusion there was a dramatic 30-fold increase in the number of circulating NK cells and an over 350-fold increase in the number of CD56bright NK cells (**Figure 2**). 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 CD56bright > CD56dim, CD94high, > CD56dim, CD94low. The functional capacity of the dominant CD56bright subset was augmented following IL-15 administration and was associated with an increase in their expression of perforin and granzyme. Furthermore, although the specific lytic activity of CD56bright cells was not as great as that of CD56dim cells, their lytic activity was

markedly increased by IL-15 treatment including activity associated with antibody-dependent cellular cytotoxicity (ADCC), as assessed in vitro by their cytotoxicity against target cells, anti-CD20 antibody coated Raji cells, K562 cells (natural cytotoxicity mediated by NKp30 and NKp46) and C1R-MICA cells (NKG2D-mediated cytotoxicity)(28). These observations on the effect of IL-15 on NK subsets and their function support the proposed trials described below that involve the combinations of IL-15 with antitumor monoclonal antibodies to increase their ADCC and antitumor efficacy.

A trial of IL-15 by civ for 5 days has been initiated, and in the 10 patients studied following treatment there was a 21 to 44-fold increase in the number of circulating NK cells, and up to an 8.9-fold increase in the number of CD8+ T cells (**Figure 2**, **Table 1**).

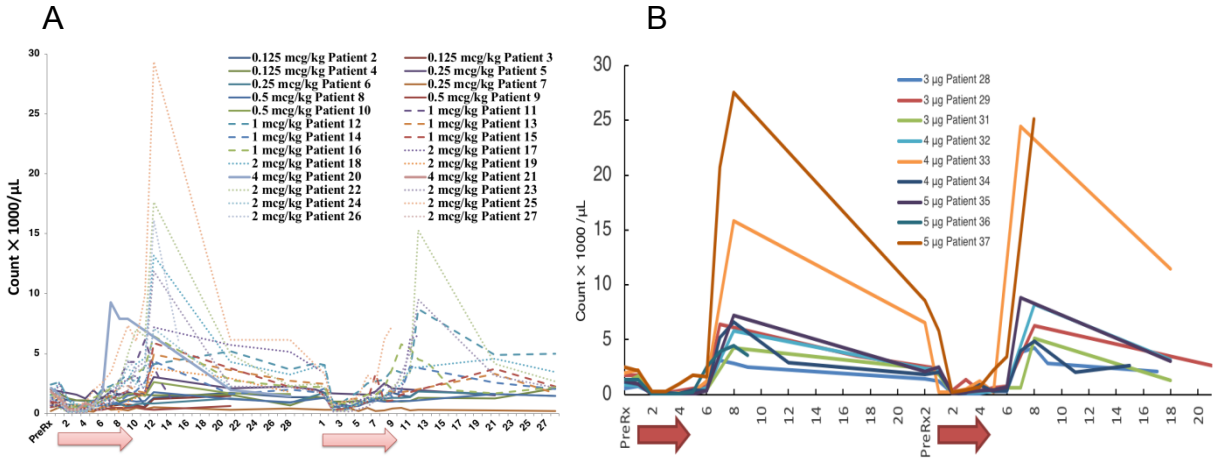


Figure 2: Increase in lymphocytes, predominantly NK cell count, during continuous infusion of rhIL-15. rhIL-15 was administered at progressively increasing doses of 0.25, 0.5, 1.0, 2.0 and 4.0 mcg/kg/day by 10-day civ infusion (A) and 5-day civ infusion (B) to patients with metastatic malignancy. Patients 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 1: 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

Diagnosis	Age	Gender	Dose level (mcg/kg)	No. of doses	NK cell increase (fold)	CD8+ T-cell increase (fold)
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

1.2.9 Avelumab

Avelumab is a fully human IgG1, anti-programmed death ligand-1 (PD-L1) antibody that inhibits PD1/PD-L1 interactions while leaving the PD1/PD-L2 pathway intact and enhances immune activation against tumor cells(29-36). Avelumab (Bavencio®) received U.S. FDA accelerated approval for the treatment of patients with metastatic Merkel cell carcinoma (MCC)(34) and urothelial carcinoma(30). Unlike other approved anti-PD-L1/PD1 antibodies, avelumab induces lysis of tumor cells via ADCC, indicating an additional mechanism of action. However, avelumab has not shown ADCC against normal immune cell subsets in humans(31). PD-L1 is found predominantly on tumor cells and binds to PD1, which like CTLA-4 is found primarily on T cells. When overexpressed in tumors, PD-L1 is a negative prognostic marker, most likely due to T-cell anergy induced by the binding of PD-L1 to PD1(37, 38). The standard therapeutic dose and dosing strategy involves 10 mg/kg IV infusion of avelumab given every 2 weeks(30).

1.2.9.1 Experience with avelumab in refractory metastatic urothelial carcinoma

Sixty-six patients with metastatic urothelial carcinoma were studied with avelumab(30). An independent central review assessment resulted in a confirmed ORR of 18.2% including 5 patients (11.4%) with a complete response (**Figure 3**). Three patients (6.8%) had a partial response and 15 patients had stable disease as best response. Patients' responses were predominantly found in those with PD-L1 positive tumors. Seven of eight responding patients (87.5%) had PD-L1 positive tumors whereas only 4.7% (1 of 24) of patients with PD-L1 negative tumors had a response. The median time to response was 13.0 weeks. The median duration of response was not reached.

1.2.9.2 Experience with avelumab in ovarian cancer

A total of 124 relapsed ovarian cancer patients were treated with avelumab resulting in a response rate of 9.7% comprised of 12 partial responses with 6 ongoing. Stable disease was observed in 44% yielding a disease control rate of 54% (unpublished data).

1.2.9.3 Experience with avelumab in non-small cell lung cancer (NSCLC)

In a Phase 1b trial of 184 patients, objective responses were observed in 22 (12%) patients, 1 CR, 21 PRs, and stable disease was found in 70 patients (38%)(39). Overall, 50% of patients achieved disease control. 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 most common being infusion reactions (2%) and increased lipase level (2%).

1.2.9.4 Experience with avelumab in breast cancer

Avelumab was studied in 168 patients with locally advanced breast cancer or MVC refractory to or progressing after standard of care. Response rate in the entire cohort was 5.4% (9 patients) with

1 complete and 8 partial responses. Stable disease was observed in an additional 40 patients (23.8%) yielding an overall disease control rate of 29.2%. Responses were predominantly in PD-L1 expressing tumors (unpublished data).

1.2.9.5 Experience of with avelumab in Merkel cell carcinoma

Merkel cell carcinoma (MCC) is a rare aggressive neuroendocrine tumor of the skin. The proportion of patients who achieved an objective response was 28/88 (31.8%) including 8 complete and 20 partial responses(34).

Further trials of avelumab for mesothelioma, gastric cancer, adrenocortical carcinoma and renal cancer are ongoing.

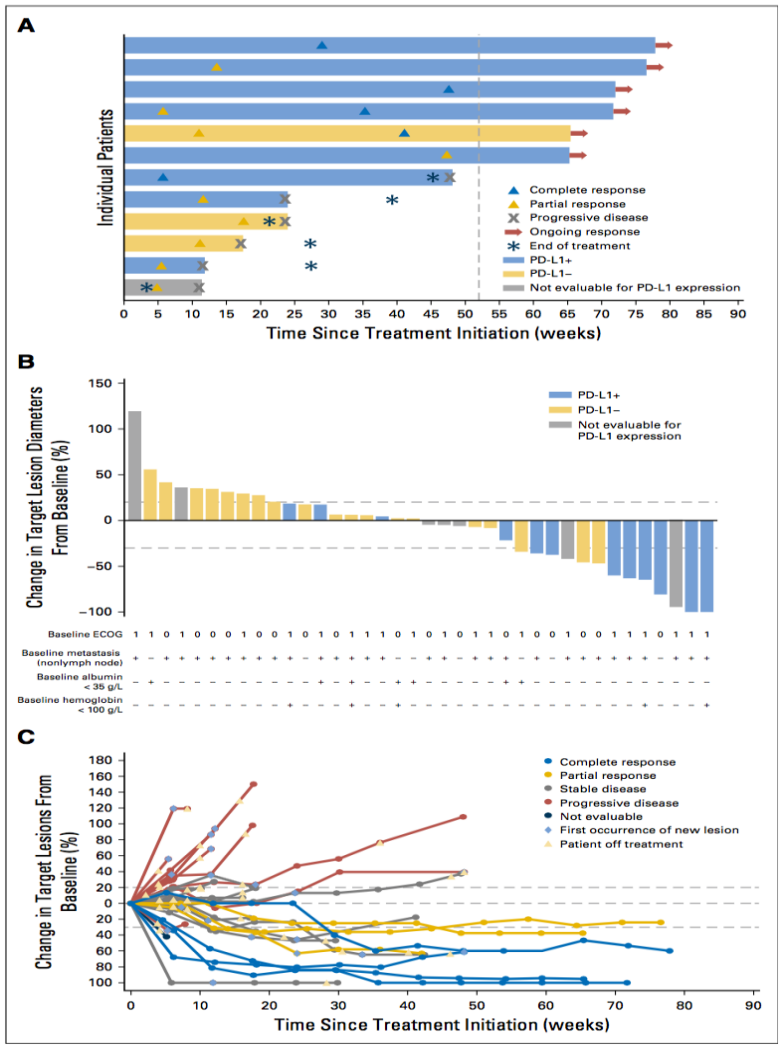


Figure 3:Clinical activity of avelumab. (A) Time to response, duration of treatment, and duration of response to avelumab (eight confirmed responses and four unconfirmed responses as of data cutoff), with PD-L1 expression status indicated (on the basis of a >5% staining threshold on tumor cells; non-evaluable 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). 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 post- baseline 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%. (30)

1.2.9.6 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).

1.2.10 Rationale of Study

1.2.10.1 PD-L1 expression in T-cell malignancies

Several IHC analyses have demonstrated that T-cell lymphomas express PD-L1. In a series of 26 cases of cutaneous T-cell lymphoma (CTCL), virtually all stages showed staining for PD-L1 in the majority of atypical lymphocytes (>50% in 5/7 stage I/II, 6/6 stage III, and 11/11 stage IV)(40). An older series of 11 patients with CTCL (stage unspecified), and 65 patients with peripheral T-cell lymphoma-NOS reported 17-27% PD-L1 positivity by immunohistochemistry with a cutoff of 30%(41). Low prevalence of PD-L1 expression in PTCL-NOS was confirmed in a series of 11 patients, with three (28%) being positive using a ≥5% cutoff(42).

Eighteen of 24 patients with ALK-negative ALCL showed PD-L1 expression as assessed by IHC using SP142 antibody (Ventana). Interestingly, FISH analysis showed no PD-L1 gene amplification, but *in silico* analysis of the PD-L1 and PD-L2 gene promoters identified multiple potential binding sites for STAT3 and MYC(43). Multiple other analyses of the T-cell lymphoma genomic landscape did not find mutations or gene copy alterations of the PD-L1-encoding PDCD1 gene(44-48). Some studies found alterations in the PD-1 encoding PDCD1 gene in 8-36% of patients with T-cell lymphoma.

Since a significant number of T-cell malignancies express PD-L1, 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.

1.2.10.2 Preclinical Trials of IL-15 with Anticancer Monoclonal Antibodies to Augment their ADCC

While the in vivo effects of IL-15 in cancer patients are still not entirely clear, the initial clinical data has demonstrated that to achieve its full potential in the treatment of cancer, IL-15 will have to be used in combination with other therapeutic agents. In light of the data from preclinical animal models and clinical trials of the capacity of IL-15 to increase the number of activated NK cells, T cells and monocytes, this information supports the administration of IL-15 with antitumor monoclonal antibodies to augment their ADCC against tumor cells. To further investigate this

strategy, the Waldmann Laboratory used an immunocompetent syngeneic mouse model of B-cell lymphoma to investigate the combination of IL-15 with rituximab. Wild-type CD56 and BL/6 mice were inoculated intravenously with EL4-CD20 cells, a mouse lymphoma line transfected with CD20. The mice were distributed into 4 treatment groups (control, IL-15 alone, rituximab alone and the combination) of 10 mice each. IL-15(5 µg/mouse) was administered 5 x per week for 4 weeks beginning 3 days after EL4-CD20 inoculation. In cohorts receiving rituximab, the monoclonal antibody was given once per week for 4 weeks starting 5 days after EL4-CD20 inoculation. As seen (**Figure 4**), IL-15 or rituximab monotherapy prolonged survival of mice when compared to the control group ($p < 0.05$) but the combination of IL-15 and rituximab showed the greatest prolongation of survival compared to monotherapies (< 0.01), such that 75 days after tumor inoculation 90% of the combination treatment group were still alive in contrast to 30% survival from the monotherapy groups and no surviving mice in the control group (**Figure 4**). In a parallel preclinical trial, the Waldmann Group administered a combination therapy of alemtuzumab with rhIL-15 in the MET-1 bearing xenograft model in wild-type SCID/NOD mice (**Figure 5**). Again, there was an augmentation of survival of the combination of IL-15 with alemtuzumab compared to either element alone. The efficacy was lost in FcRγ-/- mice, further supporting the hypothesis that the efficacy was due to augmented ADCC.

Additionally, Jochems C, et al. analyzed the in vitro ADCC capacity of an IgG1 anti-PD-L1 antibody structurally similar to avelumab with and without IL-15, and compared it to that of a fusion protein consisting of the anti-PD-L1 and a TGF-beta trap(49). IL-15/IL-15R alpha IgFc enhanced the ADCC capacity of both molecules, making them equal.

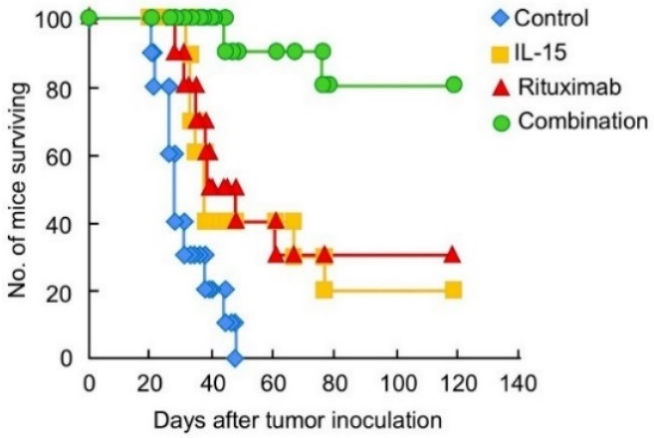


Figure 4: **Addition of IL-15 increased ADCC and antitumor efficacy of cancer-directed monoclonal antibodies.**EL4 leukemic cells were transfected with human CD20 and administered intravenously into immunologically intact mice. Mice treated with either IL-15 alone (yellow) or rituximab (anti-CD20) alone (red) showed modest prolongation of survival. This prolongation was markedly augmented when the two agents were administered together (green).

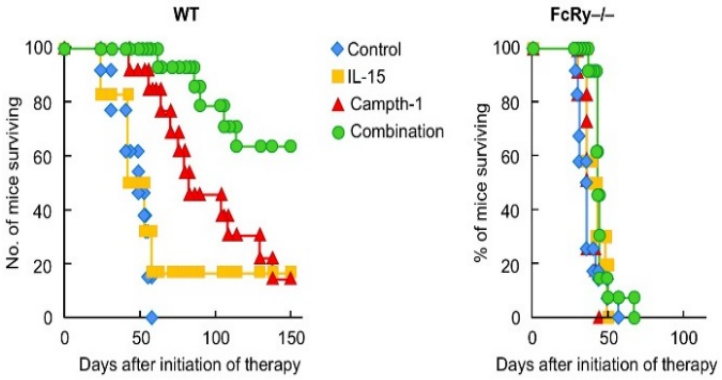


Figure 5: Combination alemtuzumab and rhIL-15 in a xenograft model of MET-1 ATL Leukemia. On the left: SCID/NOD mice bearing the MET-1 ATL leukemia who received either alemtuzumab (CAMPATH) (red) or IL-15 alone (yellow) had only modest efficacy that was markedly augmented by the combination of IL-15 plus alemtuzumab (green). Right: This efficacy was lost in FcRγ-/- mice supporting the hypothesis that the efficacy was due to ADCC.

2 ELIGIBILITY ASSESSMENT AND ENROLLMENT

2.1 ELIGIBILITY CRITERIA

2.1.1 Inclusion Criteria

2.1.1.1 Patients must have histologically or cytologically proven relapsed/refractory T-cell lymphoma other than adult T-cell leukemia/lymphoma (ATLL), angioimmunoblastic T-cell lymphoma (AITL), peripheral T-cell lymphoma T follicular helper phenotype (PTCL-TFH), or enteropathy-associated T-cell lymphoma (EATL), confirmed by the Laboratory of Pathology, NCI

2.1.1.2 Patients with CD30+ mycosis fungoides/Sézary syndrome (MF/SS) or CD30+ anaplastic large cell lymphoma (ALCL) must have relapsed after or become intolerant to treatment with brentuximab vedotin.

2.1.1.3 A formalin fixed tissue block or 15 slides of tumor sample (archival or fresh) must be available for performance of correlative studies. **NOTE:** Patients must be willing to have a tumor biopsy if prior tissue or adequate archival tissue is not available (i.e., post-enrollment and prior to treatment).

2.1.1.4 Disease must be measurable with at least one measurable lesion by RECIL 2017 or mSWAT criteria (see Section **6.3**), or have an abnormal clonal T-cell population detectable by peripheral blood flow cytometry

2.1.1.5 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 will be eligible for future pediatric trials

2.1.1.6 ECOG performance status ≤1 (Karnofsky ≥80%, see APPENDIX A).

2.1.1.7 Adequate organ and marrow function as defined below:

Absolute neutrophil count	> 1,000/mcL
Absolute lymphocyte count	≥ 500/mcL
Hemoglobin	≥ 9 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 **OR** Creatinine clearance	≤ 1.5 X institutional ULN ≥ 50 mL/min/1.73 m^2 for patients with creatinine levels >1.5 institutional ULN

2.1.1.8 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.

2.1.1.9 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 30 days 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.

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

2.1.2 Exclusion Criteria

2.1.2.1 Patients with the following T-cell leukemias/lymphomas: adult T-cell leukemia/lymphoma (ATLL), angioimmunoblastic T-cell lymphoma (AITL), peripheral T-cell lymphoma T follicular helper phenotype (PTCL-TFH), and enteropathy-associated T-cell lymphoma (EATL).

2.1.2.2 Chemotherapy and anti-tumor antibodies within 4 weeks (6 weeks for nitrosoureas or mitomycin C); other tumor-directed systemic therapy and radiation therapy within 2 weeks.

2.1.2.3 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 judgment

2.1.2.4 Patients who are receiving any other investigational agents

2.1.2.5 Patients who have had prior therapy with any antibody/drug targeting PD-1/PD-L1 T-cell coregulatory proteins (immune checkpoints)

2.1.2.6 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)

2.1.2.7 Patients with known CNS involvement 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

2.1.2.8 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

2.1.2.9 Patients with history of any organ transplantation, including allogenic stem cell transplantation

2.1.2.10 Received a live vaccine 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

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

2.1.2.12 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

2.1.2.13 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

2.1.2.14 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 **12.5** for IL-15 administration in HIV positive patients)

2.1.2.15 Patients with active or history of any autoimmune disease unrelated to their malignancy, 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

2.1.2.16 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

2.1.2.17 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

2.1.3 Recruitment Strategies

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. In addition, information will be provided on the ccr.cancer.gov/ Lymphoid-Malignancies-Branch and ClinicalTrials.gov web pages. This study will be posted on NIH websites and on NIH social media forums as well as official Lymphoid Malignancy Branch social media accounts. Study-specific public service announcements and informational fliers will be used for recruitment activities. All information to be posted or distributed publicly will be submitted to the IRB for review and approval in advance of use.

2.2 SCREENING EVALUATION

2.2.1 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

2.2.2 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 01C0129, on which screening activities will be performed.

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 Section **3.6**.

2.2.2 Clinical Evaluations

- Disease history, including: diagnosis, treatment (e.g., systemic treatments, radiation and surgeries), disease 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, and blood pressure); review of concomitant medications and symptoms/side effects; and, assessment of performance status

2.2.3 Laboratory Evaluations

NOTE: Results from outside NIH are accepted.

- CBC with differential, platelets and reticulocyte count
- Chemistry panels (as noted) or specific analyte required for eligibility, including: 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) with reflex free thyroxine (T4) per DLM policy
- Hepatitis B surface antigen (HBsAg), Hepatitis B core antibody, Hepatitis C antibody (HCV) [qualitative], HIV 1/2 antibody (qualitative) and HTLV-1/2 serologies (within 3 months) **NOTE:** For individuals with a positive hepatitis B core antibody, HBV DNA PCR will be performed to screen for subclinical infection.
- Urinalysis (with microscopic examination if abnormal)
- Antinuclear antibody (ANA), rheumatoid factor (RF) and anti-thyroid antibody
- Creatine phosphokinase (CPK), troponin
- Serum or urine pregnancy test (B-HCG) for women of childbearing potential
- Clonal T-cell receptor rearrangement by PCR

2.2.4 Imaging Studies

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

- CT neck, chest, abdomen and pelvis (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)
- MRI of brain (only in patients with suspected involvement of CNS)

2.2.5 Cardiac Evaluation (within 3 months)

- Electrocardiogram (EKG)
- Transthoracic echocardiogram

2.2.6 Other Procedures

- Pathologic review/confirmation of diagnosis by Laboratory of Pathology, NCI (no time limit). If archival sample is not available, a fresh tumor biopsy and/or peripheral blood sample will be obtained.
- Pulmonary function tests (PFTs): diffusing capacity/alveolar volume (DLCO/VA), forced expiratory volume in 1 second (FEV1) for patients with significant pulmonary or smoking history

2.3 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**.

2.3.1 Treatment Assignment Procedures

NOTE: For NCI CCR registration and enrollment system purposes only

2.3.1.1 Cohorts

Number	Name	Description
1	Mature T-cell malignancies: Dose Escalation	Relapsed/refractory T-cell lymphoma other than ATLL, AITL, PTCL-TFH, and EATL (up to 24 evaluable patients)
2	Mature T-cell malignancies: Dose Expansion	Relapsed/refractory T-cell lymphoma other than ATLL, AITL, PTCL-TFH, and EATL (up to 3 additional evaluable patients; 9 total evaluable at the MTD)

2.3.1.2 Arms

Number	Name	Description
1	Experimental Treatment: Dose Escalation	IL-15 by civ infusion at escalating doses of 1, 2, 3 and 4 mcg/kg/day on days 1-5 of each 28-day cycle (max 6 cycles) with avelumab by IV infusion at a dose of 10mcg/kg on Day 8 and 22 of each cycle, to determine MTD
2	Experimental Treatment: Dose Expansion	IL-15 by civ infusion at the MTD on days 1-5 of cycles 1-6 with avelumab at 10mcg/kg on Day 8 and 22 of each cycle

2.3.1.3 Randomization and 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.

2.4 BASELINE EVALUATION

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

2.4.1 Clinical Evaluations

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

2.4.2 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:
  - CBC with differential, platelets and reticulocyte count
  - 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, Uric acid, Total protein
    - Coagulation panel, including: PT/INR and aPTT
    - Iron panel (includes: ferritin, transferrin, iron), folate, vitamin B12
    - C-reactive protein (CRP)
    - Serum Lipase and Amylase
    - TSH with reflex free T4
    - Urinalysis (with microscopic examination if abnormal)
    - HLA typing (A, B, C, DR, DQ)
    - Soluble IL-2R
    - Creatinine phosphokinase (CPK), troponin I
- Required within 28 days:
    - Lymphocyte Phenotype: T, B and NK cell subsets
    - Antinuclear antibody (ANA), rheumatoid factor (RF) and anti-thyroid antibody

2.4.3 Imaging Studies

Every participant should have an evaluation of known sites of disease as part of baseline evaluation. **NOTE:** Only results from NIH are accepted

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

*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.

2.4.4 Other Procedures

- Bone marrow biopsy and aspiration to assess lymphoma involvement (within 3 months)
- Selected patients with cutaneous disease (as determined by physician PI or AI) will have clinical photography and dermatology assessment performed to assess their skin disease

2.4.5 Research Correlates

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

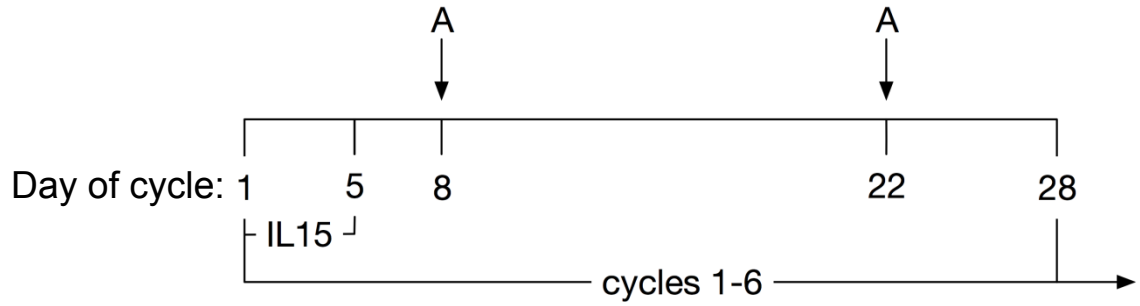
- Required:
    - Blood samples for lymphocyte subset testing and circulating tumor DNA
    - Blood, buccal swab, or saliva for germline DNA
    - Tumor Tissue (archival or fresh)

- Optional:
  - Blood samples for ADCC of avelumab, tissue immune cell subset comparison (as outlined in Section **5.1**)
  - Bone marrow biopsy
  - Tumor biopsy is required if archival tissue is not available or adequate; otherwise, this is optional.

3 STUDY IMPLEMENTATION

3.1 STUDY DESIGN

In patients with relapsed or refractory T-cell malignancies, IL-15 will be administered by continuous intravenous infusion in a dose-escalation 3 + 3 system with a starting dose of 1 mcg/kg/day, a second dose level of 2 mcg/kg/day, a third dose level at 3 mcg/kg/day, and a fourth dose level at 4 mcg/kg/day on days 1-5 of each of six cycles. Avelumab (IV over 1 hour) will be administered at a dose of 10 mg/kg on days 8 and 22 of the cycle. Treatment will continue for a maximum of 6 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.



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, 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) 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 DLT-defining toxicity after the first 28 days of treatment will lead to permanent discontinuation of protocol therapy; however, will not be deemed a DLT for purposes of dose escalation.

3.1.2 Dose Escalation

Dose escalation will proceed according to the following schedule (**Table 2**). Dose escalation will follow the following guidelines (**Table 3: Dose Escalation**). DLT is defined above. 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.

The MTD is the dose level at which no more than 1 of up to 6 patients experience DLT during the DLT evaluation window(s), or the dose below that at which at least 2 (of ≤6) patients have DLT. The protocol will be amended to note the MTD once determined.

Table 2: IL-15 Dose Escalation Schedule

Dose Level	rhIL-15 (mcg/kg)	Avelumab (mg/kg)
Level 1	1	10
Level 2	2	10
Level 3	3	10
Level 4	4	10
*Doses are stated as exact dose in units (e.g., mg/m^2, mcg/kg, etc.) rather than as a percentage.		

Table 3: Dose Escalation Guidelines

Number of Patients with DLT at a Given Dose Level	Escalation Decision Rule
0 out of 3	Enter 3 patients at the next dose level.

Number of Patients with DLT at a Given Dose Level	Escalation Decision Rule
≥2	Dose escalation will be stopped. This dose level will be declared the maximally administered dose (highest dose administered). Three (3) additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose.
1 out of 3	Enter at least 3 more patients at this dose level. • If 0 of these 3 patients experience DLT, proceed to the next dose level. • If 1 or more of this group suffer DLT, then dose escalation is stopped, and this dose is declared the maximally administered dose. Three (3) additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose.
≤1 out of 6 at highest dose level below the maximally administered dose	This is generally the recommended phase 2 dose. At least 6 patients must be entered at the recommended phase 2 dose.

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 will be 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 are described in Section **3.3**. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy. See **Table 4** below for description of drug regimen.

Table 4: Drug Regimen

Agent	Premedications; Precautions	Dose	Route	Schedule
rhIL-15	Premedicate with acetaminophen and/or ibuprofen	** in *** mL D5W with 0.1% HSA	IV over 24 hours	Days 1-5
Avelumab	Premedicate with acetaminophen and an antihistamine*	** in 250 mL 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 D** APPENDIX D				

For a full detailed product description and administration guidelines, see Section **14**. Infusions may be done peripherally or 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.

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 (including bag changes) as first line. Ibuprofen 400 or 600mg orally may be given in addition to or instead of acetaminophen, 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 20 mg 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.

3.3 DOSE MODIFICATIONS

If one study agent is held, the other must be held as well. The maximum time agents may be held cannot exceed 6 weeks. Patients who exceed 6 weeks must be removed from the study (section **3.7**).

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 **14.1.2.**

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, 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.

Note: IL-15 should not be administered within 1 week of steroid administration when steroids are given to treat avelumab toxicities as listed in the Section **3.3.2**.

3.3.2 Avelumab

3.3.2.1 Treatment modifications for symptoms of infusion-related reactions

Table 5: 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.
NOTE: 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 6: 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.
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. IV equivalent of 1 to 2 mg/kg/day prednisone 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 7: 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 0.5 to 1.0 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
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 PO, or PO/IV equivalent Add prophylactic antibiotics for opportunistic infections	If improves to Grade ≤ 1: Taper steroids over at least 1 month and add prophylactic antibiotics for opportunistic infections

Table 8: 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 PO, or PO/IV 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 ≤ 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

Pulmonary irAEs		
Pneumonitis	**Initial Management**	**Follow-up Management**
Grade 3 or 4 Grade 3: Severe new symptoms; New / worsening hypoxia Grade 4: Life-threatening	Permanently discontinue protocol therapy Hospitalize Pulmonary and Infectious Disease consults 1 to 2 mg/kg/day prednisone PO, or PO/IV equivalent Add prophylactic antibiotics for opportunistic infections Consider bronchoscopy, lung biopsy	If improves to Grade ≤ 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 9: 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 protocol therapy Increase frequency of monitoring to every 1 to 2 days 1 to 2 mg/kg/day prednisone PO, or PO/IV 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 10: 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 PO, or PO/IV 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.
Grade 4 Creatinine increased > 6 x ULN	Permanently discontinue protocol therapy Monitor creatinine daily 1 to 2 mg/kg/day prednisone PO, or PO/IV equivalent. Add prophylactic antibiotics for opportunistic infections Consider renal biopsy Nephrology consult	If improves to Grade ≤ 1: Taper steroids over at least 1 month

Table 11: 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 PO, or PO/IV 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)

Cardiac irAEs		
Myocarditis	**Initial Management**	**Follow-up Management**
*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 12: 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 $\leq$ 1 (with or without hormone replacement/suppression). Continue hormone replacement/suppression and monitoring of endocrine function as appropriate.

Endocrine irAEs		
Endocrine disorder	**Initial Management**	**Follow-up Management**
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 PO, or PO/IV 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 13: 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 PO, or PO/IV equivalent. Add prophylactic antibiotics for opportunistic infections Specialty consult as appropriate	If returns to Grade ≤ 1: Taper steroids over at least 1 month, and resume avelumab following steroids taper.

Other irAEs (not described above)		
Grade of other irAEs (NCI CTCAE v5)	**Initial Management**	**Follow-up Management**
Recurrence of same Grade 3 irAEs	Permanently discontinue protocol therapy 1 to 2 mg/kg/day prednisone PO or PO/IV equivalent. Add prophylactic antibiotics for opportunistic infections Specialty consult as appropriate	If returns to Grade ≤ 1: Taper steroids over at least 1 month
Grade 4	Permanently discontinue protocol therapy 1 to 2 mg/kg/day prednisone PO, or PO/IV equivalent and/or other immunosuppressant as needed. Add prophylactic antibiotics for opportunistic infections Specialty consult	If improves to Grade ≤ 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 protocol therapy 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.

3.4 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. 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 six cycles or until disease progression, unacceptable treatment-related toxicity or other reasons outlined in Section **3.8.1**.

Refer to the Study Calendars (Section **3.6**) 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.

3.5 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 in all subjects. 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 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 for symptoms.

Unless otherwise noted for subjects who come off treatment without evidence of disease progression, 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 2 years, then annually (±6 weeks) at the discretion of the investigator. See Section **3.5.3**. 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 (i.e., every 3 months [±4 weeks]) until the subject is off study; unless otherwise clinically indicated. See Section **3.5.4** and the Study Calendar (Section **3.6**) for additional information. Any adverse events which are present at the time of discontinuation should be followed in accordance with the safety requirements.

3.5.1 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 **3.6**). 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.

3.5.2 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 with subsequent clinic visit requested in case any concerns are noted during the telephone call.

3.5.3 Follow-Up Visits- Prior to Disease Progression

Patients who complete trial 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 2 years, then annually (±6 weeks) after finishing treatment by radiologic imaging or other clinical assessments to monitor disease status. Imaging assessment will be performed at each scheduled post-treatment follow-up visit for up to 3 years. 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.

3.5.4 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 to 6 months 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).

3.6 STUDY CALENDAR

Procedure	**Screening**	**Baseline**		**Study Cycles**							**Disease Evaluations**	**End of Treatment and Disease Progression**	**Post-Treatment Follow-Up**		
				C1				C2-6					Safety [1]	Follow-Up (Prior to PD)	Survival (Post-PD)
Scheduling Window (Days):	-28 to -1[2]		-14[3]	5 (-1)	8 (-3)	9	22 (-3)	1 (-3)	8 (-3)	22 (-3)	Every 8 weeks [4]	Treatment discon/PD [5]	Day 30 (±7)	Every 60 or 90 days [6]	Every 3 months [7]
Confirmation of Diagnosis [8]	X														
Physical Exam and ECOG PS [9]	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 [10]	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	
Uric Acid, Total Protein		X	X		X		X	X	X	X					
PT/INR and aPTT	X	X	X					X				X	X	X	
Thyroid Function (TSH, reflex free 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														
HLA typing (A, B, C, DR, DQ)		X	X												
Anti-nuclear antibody (ANA), rheumatoid factor (RF) and anti-thyroid antibody	X	X													
Clonal T-cell receptor rearrangement by PCR	X														
Iron panels, Folate, and B12, C-reactive Protein, IL-2R		X	X												
Creatine phosphokinase (CPK), troponin	X	X	X									X		X	

Procedure	**Screening**	**Baseline**		**Study Cycles**							**Disease Evaluations**	**End of Treatment and Disease Progression**	**Post-Treatment Follow-Up**		
				C1				C2-6					Safety [1]	Follow-Up (Prior to PD)	Survival (Post-PD)
Scheduling Window (Days):	-28 to -1[2]		-14[3]	5 (-1)	8 (-3)	9	22 (-3)	1 (-3)	8 (-3)	22 (-3)	Every 8 weeks [4]	Treatment discon/PD [5]	Day 30 (±7)	Every 60 or 90 days [6]	Every 3 months [7]
Pulmonary function tests (PFTs) [11]	X														
T, B, NK cell subsets		X			X			X	X			X	X	X	
Imaging studies [12]	X	X									X	X		X	
MRI, Lumbar Puncture [13]		X									X	X		X	
Bone Marrow Aspiration/Biopsy [14]		X										X	X		
Flow Cytometry[15]		X									X	X	X	X	
Clinical photography and dermatology assessment/ global score [16]		X									X	X		X	
Radiologic Evaluation/ tumor measurement[17]		X									X	X		X	
EKG. TTE	X														
Symptoms/Adverse Events Assessment, Concomitant Medication Review	X	X						X				X	X	X	
Research Blood/Tissue Samples [18]		X	X	X	X	X	X	X	X		X	X	X	X	
Survival Status															X

NOTE: Any other tests should be performed as clinically indicated. See Section **3.2** for drug administration information. See Section **5** for information on research blood samples/correlative studies to be collected.

[1] 30 days (±7) following last dose, and 90 days (+14) after last dose of avelumab (via clinic or phone). 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.

[2] 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, HTLV-1/2 serologies, Hepatitis B surface antigen and Hepatitis C antibody, EKG, and bone marrow aspiration/biopsy (all within 3 months) **NOTE:** Any screening tests performed within the specified time frame for baseline do not need to be repeated.

[3] Within 14 days prior to dosing on C1D1, with the following exceptions: Pregnancy test (within7 days of dosing; must be negative).

[4] ± 4 days, from date of prior assessment. Confirmatory scans should also be obtained 4 weeks following initial documentation of objective response. After completion of treatment, imaging assessment will be performed at each scheduled post-treatment follow-up visit for up to 3 years.

[5] 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.

[6] Follow-up to occur about every 60 days (±7 days) for first 6 months, every 90 days (±14 days) for 2 years, then every 6 months (± 28 days) for another 2 years and then annually (± 6 weeks) until disease progression or initiation of new anti-cancer therapy. After completion of treatment, imaging assessment will be performed at each scheduled post-treatment follow-up visit for up to 3 years.

[7] After disease progression or initiation of new anti-cancer therapy, contact for survival about every 3 to 6 months (±4 weeks).

[8] Pathologic review/confirmation of diagnosis by Laboratory of Pathology, NCI (no time limit). If archival sample is not available, a fresh tumor biopsy and/or peripheral blood sample will be obtained.

[9] 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). ECOG to be recorded at least once per cycle, on day 1, 8, and/or 22.

[10] Chemistry panels include: Acute care, Hepatic, and Mineral.

[11] Diffusing capacity/alveolar volume (DLCO/VA), forced expiratory volume in 1 second (FEV1) for patients with significant pulmonary or smoking history.

[12] At screening a CT scans of neck, chest, abdomen, and pelvis 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). Other body areas may be imaged if clinically indicated. MRI of the brain is only required in patients with suspected involvement of CNS. Also, at screening, a FDG-PET/CT torso (extremities to be included if there is confirmed or suspected disease involvement). At baseline one or more of the following studies: CT, MRI, FDG-PET/CT and or clinical photography.

[13] Patients with neurological symptoms or signs should undergo MRI scan of the brain and lumbar puncture.

[14] Baseline bone marrow aspiration/ biopsy with flow cytometry must be done within 3 months prior to starting treatment. During post-treatment follow-up, repeat bone marrow aspiration/ biopsy needed only to confirm a CR.

[15] Peripheral blood flow cytometry may be done for disease evaluation of patients who had circulating leukemic cells detected at baseline, and for patients with CTCL regardless of their baseline results.

[16] To be performed in selected patients with cutaneous disease (as determined by PI or AI).

[17] Dermatology assessment and Global/mSWAT scoring will be used instead of or in addition to radiologic evaluation for patients with predominantly cutaneous disease

[18] Samples for correlative research are to be collected as indicated in Section **5**. Prior biopsy specimen blocks will be used for PD-L1 staining if available. If archival tissue is not available or adequate, baseline punch biopsy of the skin or core needle biopsy of a lymph node/visceral lesion is required, otherwise this is optional.

3.7 COST AND COMPENSATION

3.7.1 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.

3.7.2 Compensation

Participants will not be compensated on this study.

3.7.3 Reimbursement

The NCI will cover the costs of some expenses associated with protocol participation. Some of these costs may be paid directly by the NIH and some may be reimbursed to the participant/guardian as appropriate. The amount and form of these payments are determined by the NCI Travel and Lodging Reimbursement Policy.

3.8 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 **3.5**.

3.8.1 Criteria for removal from protocol therapy

Patients who meet the following criteria should be discontinued from protocol therapy:

- Completion of protocol therapy (i.e., up to 6 cycles)
- Confirmed 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
- More than 6 weeks has elapsed since the patient received protocol therapy
- 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
- The drug manufacturer can no longer proved the study agent
- Study is cancelled for any reason

3.8.2 Off-Study Criteria

- Subject requests to be withdrawn from study
- Subject is lost to follow-up
- Death

- Study is cancelled for any reason

3.8.3 Lost to Follow-up

A participant will be considered lost to follow-up if he or she fails to return for two consecutive scheduled visits 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 3 business days 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, with the exception of oral or parenteral steroids if they are administered more than 7 days before the start of or more than 7 days after the end of IL-15 infusion (Note: Dexamethasone for treatment or prophylaxis of avelumab-associated infusion reactions may be administered at any time). If there is a clinical indication for a prohibited medication/ measure during the trial, discontinuation from trial therapy 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. 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

NOTE: Radiation therapy to a symptomatic solitary lesion may be allowed at the investigator's discretion.

- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, typhoid vaccine and FluMist.

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

5 CORRELATIVE STUDIES FOR RESEARCH

5.1 BIOSPECIMEN COLLECTION

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 mature T-cell malignancies. 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 D5	C1 D8	C1 D9	C1 D22	C2-6 D1	C2-6 D8	Follow-up[#]	
Blood Samples										
Lymphocyte subset testing	• 2 x 10mL K_2EDTA (lavender-top) tubes	X		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]			(X)[2]		Waldmann
Tissue immune cell subsets (comparison)	• 1 x 5mL green-top tube	(X)				(X)			(X)	Waldmann
PBMC Banking	• 3 x 10mL sodium heparin green-top tubes	X	(X)	X		X	X	X	(X)	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]	
Anti-IL-15 antibodies	• 1 x 4mL SST tube	X					X		X[1]	
Tissue Samples										
Tissue immune cell subsets	• Two core biopsy samples in RPMI 1640 with 10% human serum and antibiotics • One core biopsy sample in formalin NOTE: Samples may be tumor tissue or bone marrow aspirate/biopsy	X**				(X)			(X)	Waldmann/ (RPMI 1640) and DLM/ NCI LP (formalin)
Other Samples										
Germline DNA	• Blood, Buccal Swab, or Saliva (preferred)	X								Waldmann

(X) = Optional; samples will be collected if adequate time/staff available for processing. If an optional sample is not collected at baseline, it would also not be collected in follow-up unless specifically requested by the PI.

*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.

**Tumor biopsy is required if archival tissue is not available or adequate; otherwise, this is optional

[#]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; C1D9 and 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 **3.5.3**.

5.2 SAMPLE COLLECTION AND PROCESSING

5.2.1 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.

All samples will be delivered to the laboratory of Dr. Thomas Waldmann, Lymphoid Malignancies Branch. The laboratory staff will handle processing or delivery/shipping of associated labs, if applicable. To arrange for sample processing, contact: Bonnita Bryant, Lymphoid Malignancies Branch (Building 10, Room 3B35; phone: 240-858-3479) or Sigrid Dubois, Ph.D., Lymphoid Malignancies Branch (Building 10, Room 4B47; phone: 301-435-4441). Tissue samples will also be sent to the Hematopathology Section of the National Cancer Institute Laboratory of Pathology, by courier service.

5.2.2 Blood Samples

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

5.2.3 Lymphocyte subset testing by flow cytometry (FACS)

- Collect blood in EDTA tubes; gently invert 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.
- Lymphoid Malignancies Branch Clinical Research personnel will arrange for these samples to be delivered to: Immunology Lab, NIH Clinical Center Bldg. 10/ Room 2C410. If the Immunology Section Laboratory is unable to perform this analysis on the specified days, this assessment maybe omitted or replaced with standard TBNK panel

5.2.4 Antibody-dependent cell cytotoxicity (ADCC) of avelumab

- Collect blood in sodium heparin tubes; gently invert tubes 8-10 times immediately after collection.
- Samples will be processed per established laboratory techniques.
- Lymphoid Malignancies Branch 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, or directly to Sigrid Dubois, PhD for immediate analysis.

5.2.5 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. Plasma will be isolated and frozen at -80ºC until analysis (e.g., centrifuged at 1800 x g for 10 minutes at room temperature; plasma transferred/frozen in aliquots of 1.5-2 mL each).
- Lymphoid Malignancies Branch 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 techniques maintained within standard operating procedures in the laboratory.

5.2.5.1 Anti-IL-15 antibody testing

- Collect blood in a 4mL SST tube; gently invert tubes 8-10 times immediately after collection.
- Lymphoid Malignancies Branch 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 E** after the last patient has been enrolled and completed treatment, or sooner if there is clinical suspicion for anti-IL-15 antibody formation.

5.2.5.2 PBMC Banking

- Collect blood in sodium heparin tubes; gently invert tubes 8-10 times immediately after collection.
- Lymphoid Malignancies Branch 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 techniques maintained within standard operating procedures in the laboratory.

5.2.6 Tissue Samples

5.2.6.1 PDL-1 testing for immunohistochemistry (IHC)

- Archival block(s) or slides (i.e., at least 15 unstained slides, 5-microns) is required at baseline. Patients with prior skin, lymph node, or visceral biopsies performed at NIH or outside institutions must make specimen blocks available to the NCI Pathology Department for analysis. If no prior biopsies are available at the time of screening, patients with Cutaneous T-cell lymphoma and other lymphoma with skin involvement will undergo a punch biopsy of a skin lesion, performed by an NIH Clinical Center dermatologist. 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). An optional biopsy may be performed in the same manner prior to the second dose of avelumab (Cycle 1, Day 22).
- 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 (if needed for diagnosis) or baseline, core tumor tissue (or bone marrow aspirate/biopsy) samples will be collected and

placed in appropriate media (e.g., RPMI 1640 with 10% human serum and antibiotics, and formalin) and processed per established techniques. As indicated (Sections **5.1** and **5.2**), samples will be sent to the Department of Laboratory Medicine (DLM)/ NCI Laboratory of Pathology (LP) for concurrent routine histologic analysis and reporting and IHC testing for PD-L1 expression by tumor cells and tumor-associated immune cells in addition to research testing (i.e., Waldmann Lab).

5.2.7 Other Samples

5.2.7.1 Germline DNA

Germline DNA will be collected by blood, buccal swab, and/or saliva samples (preferred). These will ideally be collected at baseline; however, may be collected at any point on study based on supplies. Standardized, commercial collection kits or tubes will be used (e.g., 1, 5-10 mL K_2EDTA tube for blood; Isohelix SK-1 for buccal swabs; Salviette/Oragene® for saliva). In the case of buccal swabs, two (2) samples may be collected in order to ensure adequate DNA collection.

The samples will be processed and DNA extracted/isolated per kit instructions and established techniques.

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 Molecular Profiling

Immunohistochemical (IHC) analyses, including FISH and/or PCR testing, will take part in 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 for immune subsets including but not necessarily limited to CD8+ T-cells, CD4+Foxp3- T-cells, Tregs, T_{ex}, 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 and PBMC banking

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 herald progression or disease transformation; specifically, amplification and sequencing of the VDJ segment of the immunoglobulin receptor is planned. Germline DNA obtained from saliva, blood, or buccal mucosa will be used to discriminate somatic from germline mutations during cfDNA and ctDNA analyses. Keeping in mind a recent report of immune checkpoint inhibition in a patient with a solid tumor being associated with T-cell lymphomagenesis (50), and with our own group's experience with rapid progression in 3 patients with ATLL treated with ICI (22, 51), special attention will be paid to following T-cell clonality using amplification and sequencing of the complementarity determining region 3 (CDR3) in both cfDNA and banked PBMCs.

5.3.5 DNA/RNA Sequencing

Genomic DNA and total RNA will be extracted from tumor samples using a Qiagen All-prep kit. For individual target genes that are recurrently mutated in T-cell malignancies, classical Sanger sequencing will be performed on PCR amplicons, using primers surrounding the known sites of mutation. To broadly assess mutations, next generation sequencing (e.g., on an Illumina HiSeq 2000 platform) will be employed, using a paired end sequencing strategy of libraries constructed from tumor DNA. DNA will either be sequenced in its entirety from a whole genome library or will be first enriched for exonic sequences using the Agilent Sure Select system, aiming for 30X or 100X average coverage per base, respectively. The sequence fragments will be mapped back to the genome using the BWA algorithm. Of sequences overlapping a particular base pair in the genome, the percent mutant calls greater that 20% with a minimum of 25X coverage will be considered as an arbitrary threshold for single nucleotide variants (SNVs). SNVs that are not present in the matched normal sample will be considered candidate somatic mutations.

A related technology, RNA-Seq, utilizes RNA from the tumor specimen to create a cDNA library for high-throughput sequencing. RNA-seq will be performed using Illumina kits followed by high-throughput sequencing on an Illumina HighSeq 2000 machine. The cutoffs for coverage and percent mutant calls mentioned above will also be used to identify putative SNVs. RNA sequencing will also be used to read out digital gene expression across the genome as described.

Recent advances in genomic technologies enable GEP at the single cell level, a distinct advantage over conventional GEP which cannot always distinguish tumor vs non-tumor gene expression. Single-cell approaches allow identification of the evolution of rare populations of resistant tumor cells, as well as identification of TME cells critical for the survival of the tumor. The Center for Cancer Research (CCR) has recently opened a single cell analysis core facility with expert staff headed by Dr. Michael Kelly within the CCR Genomics Core. This facility has the ability to take

purified viably frozen cells banked from patient biopsies and prepare them, using well-validated 10X Genomics technology, for single-cell RNA sequencing. This core is directly integrated with the NCI Sequencing core facility to provide high-quality, deep-sequencing of the single cell RNA-SEQ samples, as well as 'first-pass' data processing and analysis. Data will then be transferred to lymphoma researchers and bio-informaticians for further analysis of gene expression patterns and cellular population dynamics.

5.3.6 Other Analyses

Other analyses include the following:

- Cell analysis and histological (e.g., H&E), immunohistochemical review and analysis per standard and established research techniques (e.g., PD-1/PD-L1 expression [Dako], FISH for del(17p), and other IHC analyses in blood and tissue).
- Cytokine analysis (e.g., IL-6, IL-10, interferon beta, TNF-alpha)

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 in section **7.2.**

5.4.2 Lymphoid Malignancies Branch – Waldmann Laboratory

Under the direction of Dr. Waldmann, all samples processed by the laboratory will be uniquely barcoded, with data entered using a secure computerized database and backup hardcopy process per standard laboratory practice.

Samples are stored in labeled boxes in secured freezers (i.e., -20ºC to -80ºC, or other, as appropriate) according to stability requirements; these freezers are located onsite. Access to stored clinical samples is restricted and limited to research personnel for approved analyses only (as per the IRB approved protocol).

Upon completion of planned analyses by the Waldmann lab, leftover samples may be stored for future analyses at the Clinical Support Laboratory, Leidos Biomedical Research, Inc.in Frederick, MD (see below).

5.4.3 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 trialsThe 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 Principal Investigator who is responsible for the collections 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.

5.4.4 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.

5.5 SAMPLES FOR GENETIC/GENOMIC ANALYSIS

5.5.1 Description of the scope of genetic/genomic analysis

The research correlates for this study are expected to include DNA/RNA sequencing of tumors, including circulating tumor (ct) DNA. In addition, whole exome sequencing may include evaluation for known lymphoma mutations. For any genetic studies performed, the results will be deposited in a database such as dbGaP per NIH requirements. Although there is controlled access to such a database, such a submission carries theoretical risks of revealing the identity of the subject. This is discussed in the consent.

5.5.2 Description of how privacy and confidentiality of medical information/biological specimens will be maximized

Confidentiality for genetic samples will be maintained as described (Section **5.4.2**). In addition, a Certificate of Confidentiality has been obtained for this study.

5.5.3 Management of Results

Subjects will be contacted if a clinically actionable gene variant is discovered. Clinically actionable findings for this study are defined as disorders appearing in the American College of Medical Genetics and Genomics recommendations for the return of incidental findings that is current at the time of primary analysis. (A list of current guidelines is maintained on the CCR intranet: https://ccrod.cancer.gov/confluence/display/CCRCRO/Incidental+Findings+Lists).

5.5.4 Genetic Counseling

Subjects will be contacted with a request to provide a blood sample to be sent to a CLIA certified laboratory. If the research findings are verified in the CLIA certified lab, the subject will be offered the opportunity to come to NIH to have genetic education and counseling to explain this result; at the time of any such event(s), these activities will be funded by the NCI/CCR in consideration of the specific circumstances. If the subject does not want to come to NIH, a referral to a local genetic healthcare provider will be provided (at their expense).

This is the only time during the course of the study that incidental findings will be returned. No interrogations regarding clinically actionable findings will be made after the primary analysis.

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 through 30 days after the last study intervention was administered. Beyond 30 days after the last intervention, 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**.

6.1.2 Data Collection/Recording 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

Unlinked genomic data will be deposited in public genomic databases such as dbGaP in compliance with the NIH Genomic Data Sharing Policy.

6.3 RESPONSE CRITERIA

6.3.1 Response Assessments

Tumor response will be assessed by the investigator using the RECIL 2017 criteria (52) for all patients with T-cell lymphoma other than CTCL. Global Response Score (53), and modified severity weighted assessment tool (mSWAT) (11) will be used for patients with CTCL. Patient will be re-evaluated for response as outlined in the Study Calendar, Section **3.6**.

6.3.2 Response Criteria for PTCL and ALCL

RECIL 2017 criteria (52) use the Deauville five-point scale for assessment of response via FDG-PET. The five-point scale (5-PS) has been validated for use at interim staging and at the end of treatment and was adopted as the preferred reporting method at the First International Workshop on PET in Lymphoma in Deauville, France (i.e., Deauville criteria), and in several international trials.

The 5-PS PS scores the most intense uptake in a site of initial disease:

1. if present, as follows: no uptake or no residual uptake (when used at interim)
2. slight uptake, but below blood pool (mediastinum)
3. uptake above mediastinal, but below or equal to uptake in the liver
4. uptake slightly to moderately higher than liver
5. markedly increased uptake or any new lesion (on response evaluation)

The sum of longest diameter (SLD) is used for assessment of tumor burden. In patients with disseminated disease, a maximum of three target lesions should be selected and used to estimate tumor response. Target lesions should be selected from those with the largest size that can be reproducibly measured and preferably representing multiple sites and/organs. In most cases, lymph nodes can be considered target lesions if the lymph node longest diameter measures ≥15 mm. A lymph node measuring between 10 and 14 mm is considered abnormal but should not be selected as a target lesion. Lymph nodes measuring <10 mm in diameter are considered normal. In certain anatomical sites (inguinal, axillary, and portocaval), normal lymph nodes may exist in a narrow, elongated form, and such nodes should not be selected as target lesions if alternatives are available. Extranodal lesions are selected as target lesions if they have soft tissue component, based on their size, and the ease of reproducibility of repeated measurements, with a minimum measurement of the longest diameter of ≥ 15 mm. All other lesions should be identified as nontarget lesions and should be recorded at baseline, without the need to measure them. Nontarget lesions should be followed and reported as present, absent, or clear progression.

Table 14: Response categories based on assessment of target lesions

	% Change in sum of diameters of target lesions from nadir				
	CR	PR	MR	SD	PD
% change from baseline	• Complete disappearance of all target lesions and all nodes with long axis <10mm • ≥30% decrease in the sum of longest diameters of target lesions (PR) with normalization of FDG-PET	≥30% decrease in the sum of longest diameters of target lesions but not a CR	≥10% decrease in the sum of longest diameters of target lesions but not a PR (<30%)	<10% decrease or ≤ 20% increase in the sum of longest diameters of target lesions	• >20% increase in the sum of longest diameters of target lesions • For small lymph nodes measuring <15 mm post therapy, a minimum absolute increase of 5 mm and the long diameter should exceed 15 mm • Appearance of a new lesion
FDG-PET	Normalization of FDG-PET (Deauville score 1-3)	Positive (Deauville score 4-5)	Any	Any	Any
Bone marrow involvement	Not involved	Any	Any	Any	Any
New lesions	No	No	No	No	Yes or No

CR, complete response; CT, computerized tomography; FDG-PET, [18F]2-fluoro-2-deoxy-D-glucose; MR, minor response; PD, progression of disease; PR, partial response; SD, stable disease.

6.3.3 Response Criteria for CTCL

Global Response (GR) score (**APPENDIX C**) will be used for assessing response in patients with CTCL (53). GR score incorporates separate responses in each component of the TNBM staging (i.e., skin, nodes, viscera and blood; **APPENDIX C**). No patient with a global OR should have less than a PR in the skin.

The mSWAT (11) is an instrument utilized to track the skin tumor burden in MF/SS. It measures the percentage total body-surface area (TBSA, %) involvement separately for patches, plaques, and tumors within 12 body regions using the patient's palm and fingers representing 1% of TBSA. Patients with erythroderma are assessed for percentage of TBSA involved with patches and/or plaques. The percentage of TBSA for each lesion type is multiplied by a number (patch = 1, plaque = 2; tumor = 4) and summed to derive the mSWAT score. The mSWAT for each patient will be determined by the same individual at all study visits.

A complete response (CR) requires 100% clearing of skin disease and a partial response (PR) requires ≥ 50% reduction in the mSWAT score compared with baseline. CR/PR requires confirmation by repeat assessment after ≥ 4 weeks. Stable disease is defined as less than 50% reduction to less than 25% increase in the mSWAT score compared with baseline. PD is defined as ≥ 25% increase in the mSWAT score from baseline or ≥ 50% increase in the sum of the products of the greatest diameters of pathologically positive lymph nodes compared with baseline.

Time to response is the time from the first treatment dose until the patient first meets the criteria for a 50% decrease in the GR score. The duration of response (DOR) is the time from first CR/PR until the GR score is increased from nadir to more than 50% of the difference between the baseline and nadir scores. Time to progression (TTP) is the time from start of treatment until PD. If patients goes off treatment for any purpose, this date is used for determination of TTP and/or DOR.

As "skin flares" have been described in patients with SS receiving the anti-PD-1 antibody Pembrolizumab (18), patients with SS whose only sign of PD is an increase in mSWAT score (i.e., who have normal/decreasing number of circulating Sézary cells) will continue treatment and be re-evaluated in 2-4 weeks to confirm disease progression. Patients whose PD is not confirmed on re-evaluation will be noted to have had a skin flare

Table 15: Calculating mSWAT Score

Body Region	% BSA in Body Region	Assessment of Involvement in Patient's Skin		
		Patch[1]	Plaque[2]	Tumor[3]
Head	7			
Neck	2			
Anterior trunk	13			
Arms	8			
Forearms	6			
Hands	5			
Posterior trunk	13			
Buttocks	5			
Thighs	19			
Legs	14			
Feet	7			
Groin	1			
Subtotal of lesion BSA				

Weighing factor		x1	x2	x4
Subtotal lesion BSA x weighing factor				

NOTE: mSWAT score equals summation of each column line.

Abbreviations: BSA, body surface area; mSWAT, modified Severity Weighted Assessment Tool.

[1] Any size lesion without induration or significant elevation above the surrounding uninvolved skin; poikiloderma may be present

[2] Any size lesion that is elevated or indurated; crusting, ulceration, or poikiloderma may be present.

[3] Any solid or nodular lesion ≥ 1cm in diameter with evidence of deep infiltration in the skin and/or vertical growth.

6.3.4 Rapid progression

As recent preclinical data has shown that PD-1 may act as a tumor suppressor in T-cell malignancies(21), and three patients with ATLL who received the anti-PD-1 antibody Nivolumab experienced progression of disease shortly after receiving the first dose (NCT02631746, unpublished data), rapid progression will be followed as a distinct outcome. Rapid progression is defined as any PD within 14 days of the first avelumab administration (i.e., up to and including Cycle 1, Day 21), excluding skin flares. Patients who are suspected of having a skin flare during this period but have confirmed PD on re-evaluation will be noted to have had rapid progression.

6.3.5 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.

6.3.6 Duration of Response

The duration of response (DOR) is measured from the time measurement criteria are met for CR or PR (whichever is recorded first) 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), death, or, in the absence of PD, date of last assessment.

6.3.7 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.

6.3.8 Overall Survival

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

6.3.9 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 lymphoma given (such as radiation), or death, whichever occurs first.

6.4 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/ IRB REPORTING

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**.

7.3 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.

7.4 NIH REQUIRED DATA AND SAFETY MONITORING PLAN

7.4.1 Principal Investigator/Research Team

The clinical research team will meet at least weekly 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

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 **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 reaction 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 Product

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 with the exception of any listed in section **8.4**.

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 CRITERIA TO THE PHARMACEUTICAL COLLABORATORS AND MANUFACTURERS

All events listed below must be reported in the defined timelines to OSROsafety@mail.nih.gov. The CCR Office of Regulatory Affairs will send all reports to the manufacturer(s) as described below.

8.5.1 Safety Reporting to the Pharmaceutical Collaborator EMD Serono (Avelumab)

The investigational agent, avelumab, is being supplied by EMD Serono and the following are their requirements for safety reporting.

The following reportable events must be submitted to EMD Serono within 2 business days or 3 calendar days (whichever comes first) using the applicable safety report form provided. The Principal Investigator/study team will submit reportable events to the Sponsor as well as ensure that any other local reporting requirements are completed, if required (e.g., IRB). The Sponsor will assume responsibility for submitting the reportable event(s) to EMD Serono as well as ensuring that any local reporting requirements are completed in parallel.

- Serious Adverse Event Reports
- Exposure during pregnancy or breastfeeding (even if not associated with an adverse event)
- Occupational exposure (even if not associated with an adverse event)
- Potential drug-induced liver injury (Hy's Law cases): These events are considered important medical events and should be reported as SAEs.

Contact information for submission of reportable events to EMD Serono:

Fax: +49 6151 72 6914 or Email: ICSR_CT_GPS@merckgroup.com.

The following items should be specified:

1. Protocol Number and/or Title
2. EMD Serono assigned Study Number
3. Subject number
4. Site number/PI name

8.5.1.1 Second Malignancies

A second malignancy is one unrelated to the treatment of a prior malignancy (and is **NOT** a metastasis from the initial malignancy). Second malignancies require **ONLY** routine AE reporting unless otherwise specified.

8.5.2 Safety/Other Reporting Criteria to the Manufacturer Collaborator CTEP (rhIL-15)

The NCI Cancer Therapy Evaluation Program (CTEP) is providing clinical grade recombinant human IL-15 for this study. Because CTEP is responsible for the Clinical Material and Confidential Information which it develops, CTEP must ensure that the Clinical Material and Confidential Information are used, communicated and reproduced appropriately and completely. The PI agrees to use the Clinical Material in accordance with all Federal laws and regulations that govern the use of investigational agents in clinical trials.

The following will be provided to CTEP during the course of the clinical study:

1. Initial FDA submission/approval, including: FDA-submitted protocol document; any FDA comments regarding the protocol and IND submission, including correspondence regarding the IND submission safe-to-proceed notice; and, a copy of the FDA acknowledgement of the IND submission(s) stating the IND number, sponsor, title and date of submission.
2. Documentation of initial IRB approval of the FDA-submitted protocol document and annual continuing IRB review approvals.
3. All significant protocol amendments, including changes in study size, eligibility criteria, study design and end points.
4. Notification of any changes in protocol status or other significant events related to the Protocol.
5. Notification of any changes in IND status.
6. Copies of any FDA communications.
7. Copies of IND Annual Reports.
8. All IND Safety Reports submitted to the FDA per 21 CFR 312.32. 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).
9. Any abstracts, manuscripts, and publications.

Additional safety and efficacy data may also be requested by CTEP to facilitate the development of the Clinical Material across CTEP supported trials.

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 becomes 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 rhIL-15 and/ or 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 four months 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 HYPOTHESIS

- Primary Endpoint(s):

  - Maximum tolerated dose (MTD) of rhIL-15 administered intravenously for 5 days in combination with avelumab for up to 6 cycles
  - Frequency (number and percentage) of treatment-emergent AEs

- Secondary Endpoint(s):
  - Overall response rate (including CR and PR)
  - Overall response rate in patients with ≥50% PD-L1-expressing tumor cells
  - Duration of response
  - Progression-free, event-free, and overall survival

10.2 SAMPLE SIZE DETERMINATION

The MTD will be based on the assessment of DLT during the first cycle of treatment and will be defined as the dose level at which less than one-third of patients (0 of 3 or 0-1/6 patients) treated experience a DLT, with the next higher dose level demonstrating one-third or a greater number of patients (≥ 2-3 or ≥ 2-6 patients) having a DLT. If a subject did not experience a DLT and did not finish one cycle of treatment (28 days) he or she will not be evaluable for determination of the MTD and would be replaced in the dose level. An additional 3 to 6 patients will be enrolled at the MTD, so that a total of 9 patients will be treated at this dose.

Using this dose-escalation scheme the probability of escalating to the next dose level will be based on the true rate of DLT at the current doses given by the following table (each group will be considered independently of the other); Thus, if the true underlying proportion of DLTs is 50% at the current dose there is a 17% probability of escalating to the next dose.

True toxicity at a given dose	10%	20%	30%	40%	50%	60%
Probability of escalating	0.91	0.71	0.49	0.31	0.17	0.08

If all four dose levels are evaluated with 6 patients per dose level and 9 total patients at the MTD, a maximum of 27 evaluable patients will be enrolled. Similarly, if all dose levels are evaluated with 3 patients per dose level and 9 total patients at the MTD, the minimum number of evaluable patients required will be 18. To account of unevaluable patients, accrual ceiling will be set at 30. It is expected that the accrual can be completed in 24 months.

A maximum of 30 patients will be enrolled over 24 months, at a rate of 1-2 patients per month.

10.3 POPULATION FOR ANALYSIS

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, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These 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 Non-Target Disease Response:

Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. 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% Agresti-Coull confidence interval (54). Other time-to-event outcomes will be reported using Kaplan-Meier curves.

10.4.2 Analysis of the Primary Endpoints

Safety summaries will include summaries in the form of tables and listings. Reports will include the frequency (number and percentage) of treatment emergent AEs grouped by severity of the AE (per CTCAE, v5.0) and by relationship to study drug (e.g., either rhIL-15, avelumab, or both).

Laboratory shift tables containing counts and percentages will be prepared by treatment assignment, laboratory parameter, and time. Summary tables will be prepared for each laboratory parameter. Figures of changes in laboratory parameters over time will be generated.

Results of vital sign assessments, ECGs, and physical exams will be tabulated and summarized.

10.4.3 Analysis of the Secondary Endpoints

The duration of response (DOR; beginning at the date clinical response is first identified), overall survival (OS), event free survival (EFS), and progression free survival (PFS) will be estimated using Kaplan-Meier curves with appropriate confidence intervals reported.

Every report of response rates and time to progression should contain all patients included in the study. For the response calculation, the report should contain at least a section with all eligible patients. Another section of the report may detail the response rate for evaluable patients only. However, a response rate analysis based on a subset of patients must explain which patients were excluded and for which reasons. 95% confidence limits will be given.

10.4.4 Safety Analyses

The type, grade and frequency of toxicities will be reported.

10.4.5 Baseline Descriptive Statistics

Descriptive statistics (including means, standard deviations, and medians for continuous variables and proportions and CIs for discrete variables) will be used to summarize data as appropriate.

10.4.6 Planned Interim Analyses

No interim analyses are planned because of the single stage design of the trial.

10.4.7 Sub-Group Analyses

All secondary endpoints will be analyzed and reported separately according to the presenting diagnosis (PTCL-NOS, MF/SS, ALCL, or Other) and baseline PD-L1 expression (<1%, ≥1%, ≥5%, ≥10%, ≥50%).

10.4.8 Tabulation of Individual Participant Data

None.

10.4.9 Exploratory Analyses

The exploratory objectives such as seeking to identify potential biomarkers or T-cell clones in peripheral blood which are associated with response, will be assessed using descriptive statistics as well as non-parametric methods such as exact Wilcoxon rank sum tests. The analyses will be done without formal adjustment for multiple comparisons, but in the context of the number of tests performed.

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.

11.2 MATERIAL TRANSFER AGREEMENT (MTA)- CTEP

A MTA with Division of Cancer Treatment and Diagnosis (DCTD) for the IL-15 was executed on June 8, 2018 .

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. Subjects with HIV infection will be excluded due to potential toxicity and unknown effects of rhIL-15 and avelumab on the underlying HIV infection and interference with ART. Pregnant or nursing mothers are excluded because of the potential teratogenic effects of therapy.

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 recurrent T-cell lymphomas are 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 PARTICIPATION OF SUBJECTS UNABLE TO GIVE CONSENT

Adults who are unable to consent are excluded from enrolling in this study. However, re-consent may be necessary and there is a possibility, though unlikely, that subjects could become decisionally impaired. For this reason and because there is a prospect of direct benefit from research participation (Section **12.5**) and because overall survival is one of the secondary outcomes, all subjects ≥ age 18 will be offered the opportunity to fill in their wishes for research and care, and assign a substitute decision maker on the "NIH Advance Directive for Health Care and Medical Research Participation" form so that another person can make decisions about their medical care in the event that they become incapacitated or cognitively impaired during the course

of the study.

Note: The PI or AI will contact the NIH Ability to Consent Assessment Team (ACAT) for evaluation to assess ongoing capacity of the subjects and to identify a LAR, as needed.

Please see Section **12.6** for consent procedure.

12.4 Evaluation of Benefits and Risks/Discomforts

The potential benefit of adding rhIL-15 to avelumab in treatment of mature T-cell malignancies is unknown, but single-agent immune checkpoint inhibitors have shown activity as outlined in Section **1.2.5**. There is a risk of additive toxicity of the two drugs, 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.

It has recently been shown that PD-1 may act as a haplo-insufficient tumor suppressor of T lymphocytes, with PD-1/PD-L1 checkpoint blockade causing transient lymphoproliferation in ITK-SYK transgenic mice(21). Clinically, three patients with ATLL treated with the anti-PD-1 antibody Nivolumab had rapid disease progression shortly after receiving the first dose ("rapid progression"). Additionally, four patients with AITL have experienced rapid progression after 1-3 doses of nivolumab.(19) Patients with ATLL, AITL, and PTCL-TFH (which has a similar phenotype to AITL) are therefore excluded from this Phase 1 trial. Additionally, growth of malignant cells in enteropathy-associated T-cell lymphoma (EATL) is dependent on epithelial cell-derived IL-15. Patients with EATL are therefore also excluded. There are ongoing trials of different immune checkpoint inhibitors in patients with other forms of T cell lymphoma with no reports of rapid progression. Study team will note any rapid and unexpected disease progression observed in patients on the trial as described in Section **6.3.4**.

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(55). 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.

12.5 Risks/Benefits Analysis

A significant number of T-cell malignancies express PD-L1, 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.

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 in this study.

12.5.1 Risks related to CT and PET scans

CT and PET 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.

12.5.2 Risks from Radiation Exposure

The procedures for performing the chest CT and ^{18}F-FDG PET/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 six (6) additional CT scans of the neck, chest, abdomen, and pelvis, and three (3) additional ^{18}F-FDG PET/CT scans.

The total additional radiation dose for research purposes will be approximately 11.4 rem.

12.6 CONSENT PROCESS AND DOCUMENTATION

The informed consent document will be provided as a physical or electronic document to the participant or consent designee(s) 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/consent designee(s). Whether in person or remote, the privacy of the subject will be maintained. Consenting investigators (and participant/consent designee, when in person) will be located in a private area (e.g., clinic consult room). When consent is conducted remotely, the participant/consent designee will be informed of the private nature of the discussion and will be encouraged to relocate to a more private setting if needed.

Consent will be documented with required signatures on the physical document (which includes the printout of an electronic document sent to participant) or as described below, with a manual (non-electronic signature) on the electronic document. When required, witness signature will be obtained similarly as described for the investigator and participant.

<u>Manual (non-electronic) signature on electronic document</u>:

When a manual signature on an electronic document is used for the documentation of consent at the NIH Clinical Center, this study will use the following to obtain the required signatures:

- Adobe platform (which is not 21 CFR Part 11 compliant); or,
- iMedConsent platform (which is 21 CFR Part 11 compliant)

During the consent process, participants and investigators will view individual copies of the approved consent document on screens at their respective locations (if remote consent); the same screen may be used when in the same location but is not required.

Both the investigator and the participant will sign the document using a finger, stylus or mouse.

Note: Refer to the CCR SOP PM-2, Obtaining and Documenting the Informed Consent Process for additional information (e.g., verification of participant identity when obtaining consent remotely) found **here**.

12.6.1 Consent Process for Adults Who Lack Capacity to Consent to Research Participation

For participants addressed in Section **12.3**, an LAR will be identified consistent with Policy 403 and informed consent obtained from the LAR, as described in Section **12.6.**

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 study participants, investigator, the Investigational New Drug (IND) sponsor and regulatory authorities. 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 as applicable, Food and Drug Administration (FDA).

13.2 QUALITY ASSURANCE AND QUALITY CONTROL

Each 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 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 d 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 clinical sites 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 NCI CCR.

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

This study is being conducted under a CCR-held IND: IND #140549.

14.1 rhIL-15 (NSC #745101)

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. 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 stores 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) to reach a final rhIL-15 concentration of 1 mcg/mL (see Dilution instructions, **APPENDIX D**). 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 2-6, 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 4** 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	
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	

Adverse Events with Possible Relationship to Recombinant Human IL-15 (CTCAE 5.0 Term)	Specific Protocol Exceptions to Expedited Reporting (SPEER)
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; Visceral arterial ischemia

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Edema face; 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; Infusion related reaction

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

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 order 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 (NSC #799232)

14.2.1 Source / Acquisition and Accountability

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

14.2.2 Toxicity

Please refer to the IB 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[1]

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]	

Adverse Events with Possible Relationship to Avelumab (CTCAE 5.0 Term) [n= 1738]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
EYE DISORDERS		
		Uveitis[2]
GASTROINTESTINAL DISORDERS		
	Abdominal pain	
		Colitis[2]
	Diarrhea	
	Nausea	
	Pancreatitis[2]	
	Vomiting	
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	
	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	

Adverse Events with Possible Relationship to Avelumab (CTCAE 5.0 Term) [n= 1738]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
	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	
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	

[1]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 8 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.

15 REFERENCES

1. Project TN-HsLC. A Clinical Evaluation of the International Lymphoma Study Group Classification of Non-Hodgkin's Lymphoma. Blood. 1997;89(11):3909-18.

2. Project IT-CL. International Peripheral T-Cell and Natural Killer/T-Cell Lymphoma Study: Pathology Findings and Clinical Outcomes. Journal of Clinical Oncology. 2008;26(25):4124-30.

3. Adams SV, Newcomb PA, Shustov AR. Racial Patterns of Peripheral T-Cell Lymphoma Incidence and Survival in the United States. Journal of Clinical Oncology. 2016;34(9):963-71.

4. Carson KR, Horwitz SM, Pinter-Brown LC, Rosen ST, Pro B, Hsi ED, et al. A prospective cohort study of patients with peripheral T-cell lymphoma in the United States. Cancer. 2017;123(7):1174-83.

5. Ellin F, Landstrom J, Jerkeman M, Relander T. Real-world data on prognostic factors and treatment in peripheral T-cell lymphomas: a study from the Swedish Lymphoma Registry. Blood. 2014;124(10):1570-7.

6. Yang YT, Tai CJ, Chen C, Wu HC, Mikhaylichenko N, Chiu HT, et al. Highly Diverse Efficacy of Salvage Treatment Regimens for Relapsed or Refractory Peripheral T-Cell Lymphoma: A Systematic Review. PloS one. 2016;11(10):e0161811.

7. O'Connor OA, Pro B, Pinter-Brown L, Bartlett N, Popplewell L, Coiffier B, et al. Pralatrexate in patients with relapsed or refractory peripheral T-cell lymphoma: results from the pivotal PROPEL study. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2011;29(9):1182-9.

8. O'Connor OA, Horwitz S, Masszi T, Van Hoof A, Brown P, Doorduijn J, et al. Belinostat in Patients With Relapsed or Refractory Peripheral T-Cell Lymphoma: Results of the Pivotal Phase II BELIEF (CLN-19) Study. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2015;33(23):2492-9.

9. Coiffier B, Pro B, Prince HM, Foss F, Sokol L, Greenwood M, et al. Results from a pivotal, open-label, phase II study of romidepsin in relapsed or refractory peripheral T-cell lymphoma after prior systemic therapy. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2012;30(6):631-6.

10. Duvic M, Hymes K, Heald P, Breneman D, Martin AG, Myskowski P, et al. Bexarotene is effective and safe for treatment of refractory advanced-stage cutaneous T-cell lymphoma: multinational phase II-III trial results. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2001;19(9):2456-71.

11. Olsen EA, Kim YH, Kuzel TM, Pacheco TR, Foss FM, Parker S, et al. Phase IIb multicenter trial of vorinostat in patients with persistent, progressive, or treatment refractory cutaneous T-cell lymphoma. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2007;25(21):3109-15.

12. Piekarz RL, Frye R, Turner M, Wright JJ, Allen SL, Kirschbaum MH, et al. Phase II multi-institutional trial of the histone deacetylase inhibitor romidepsin as monotherapy for

patients with cutaneous T-cell lymphoma. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2009;27(32):5410-7.

13. Whittaker SJ, Demierre MF, Kim EJ, Rook AH, Lerner A, Duvic M, et al. Final results from a multicenter, international, pivotal study of romidepsin in refractory cutaneous T-cell lymphoma. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2010;28(29):4485-91.

14. Kim YH, Bagot M, Pinter-Brown L, Rook AH, Porcu P, Horwitz SM, et al. Mogamulizumab versus vorinostat in previously treated cutaneous T-cell lymphoma (MAVORIC): an international, open-label, randomised, controlled phase 3 trial. The Lancet Oncology. 2018;19(9):1192-204.

15. Prince HM, Kim YH, Horwitz SM, Dummer R, Scarisbrick J, Quaglino P, et al. Brentuximab vedotin or physician's choice in CD30-positive cutaneous T-cell lymphoma (ALCANZA): an international, open-label, randomised, phase 3, multicentre trial. Lancet (London, England). 2017;390(10094):555-66.

16. Pro B, Advani R, Brice P, Bartlett NL, Rosenblatt JD, Illidge T, et al. Brentuximab Vedotin (SGN-35) in Patients With Relapsed or Refractory Systemic Anaplastic Large-Cell Lymphoma: Results of a Phase II Study. Journal of Clinical Oncology. 2012;30(18):2190-6.

17. Lesokhin AM, Ansell SM, Armand P, Scott EC, Halwani A, Gutierrez M, et al. Nivolumab in Patients With Relapsed or Refractory Hematologic Malignancy: Preliminary Results of a Phase Ib Study. Journal of Clinical Oncology. 2016;34(23):2698-704.

18. Khodadoust MS, Rook AH, Porcu P, Foss F, Moskowitz A, Shustov AR, et al. Pembrolizumab For Treatment Of Relapsed/Refractory Mycosis Fungoides And Sézary Syndrome: Clinical Efficacy In A CITN Multicenter Phase 2 Study. 3rd World Congress of Cutaneous Lymphomas. 2016;Abstract O-10.

19. Bennani NN. A Phase II Study of Nivolumab in Patients with Relapsed or Refractory Peripheral T-Cell Lymphoma. ASH. 2019.

20. Pritchett J. Malignant T-Cells and Normal Intratumoral T-Cells Have Similar Expression of Immune Checkpoint Molecules in Angioimmunoblastic T-Cell Lymphoma. ASH. 2019.

21. Wartewig T, Kurgyis Z, Keppler S, Pechloff K, Hameister E, Öllinger R, et al. PD-1 is a haploinsufficient suppressor of T cell lymphomagenesis. Nature. 2017;552:121.

22. Rauch DA, Conlon KC, Janakiram M, Brammer JE, Harding JC, Ye BH, et al. Rapid Progression of Adult T-Cell Leukemia/Lymphoma as Tumor Infiltrating Treg Cells after PD-1 Blockade. Blood. 2019:blood.2019002038.

23. Conlon KC, Lugli E, Welles HC, Rosenberg SA, Fojo AT, Morris JC, et al. Redistribution, hyperproliferation, activation of natural killer cells and CD8 T cells, and cytokine production during first-in-human clinical trial of recombinant human interleukin-15 in patients with cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2015;33(1):74-82.

24. Lugli E, Goldman CK, Perera LP, Smedley J, Pung R, Yovandich JL, et al. Transient and persistent effects of IL-15 on lymphocyte homeostasis in nonhuman primates. Blood. 2010;116(17):3238-48.

25. Waldmann TA. The biology of interleukin-2 and interleukin-15: implications for cancer therapy and vaccine design. Nature reviews Immunology. 2006;6(8):595-601.

26. Waldmann TA. The biology of IL-15: implications for cancer therapy and the treatment of autoimmune disorders. The journal of investigative dermatology Symposium proceedings. 2013;16(1):S28-30.

27. Waldmann TA, Lugli E, Roederer M, Perera LP, Smedley JV, Macallister RP, et al. Safety (toxicity), pharmacokinetics, immunogenicity, and impact on elements of the normal immune system of recombinant human IL-15 in rhesus macaques. Blood. 2011;117(18):4787-95.

28. Dubois S, Conlon KC, Müller JR, Hsu-Albert J, Beltran N, Bryant BR, et al. IL15 Infusion of Cancer Patients Expands the Subpopulation of Cytotoxic CD56^{bright} NK Cells and Increases NK-Cell Cytokine Release Capabilities. Cancer immunology research. 2017;5(10):929-38.

29. Srour SA, Milton DR, Bashey A, Karduss-Urueta A, Al Malki MM, Romee R, et al. Haploidentical Transplantation with Post-Transplantation Cyclophosphamide for High-Risk Acute Lymphoblastic Leukemia. Biology of Blood and Marrow Transplantation. 2017;23(2):318-24.

30. Apolo AB, Infante JR, Balmanoukian A, Patel MR, Wang D, Kelly K, et al. Avelumab, an Anti-Programmed Death-Ligand 1 Antibody, In Patients With Refractory Metastatic Urothelial Carcinoma: Results From a Multicenter, Phase Ib Study. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2017;35(19):2117-24.

31. Boyerinas B, Jochems C, Fantini M, Heery CR, Gulley JL, Tsang KY, et al. Antibody-Dependent Cellular Cytotoxicity Activity of a Novel Anti-PD-L1 Antibody Avelumab (MSB0010718C) on Human Tumor Cells. Cancer immunology research. 2015;3(10):1148-57.

32. Grenga I, Donahue RN, Lepone LM, Richards J, Schlom J. A fully human IgG1 anti-PD-L1 MAb in an in vitro assay enhances antigen-specific T-cell responses. Clinical & translational immunology. 2016;5(5):e83.

33. Heery CR, O'Sullivan-Coyne G, Madan RA, Cordes L, Rajan A, Rauckhorst M, et al. Avelumab for metastatic or locally advanced previously treated solid tumours (JAVELIN Solid Tumor): a phase 1a, multicohort, dose-escalation trial. The Lancet Oncology. 2017;18(5):587-98.

34. Kaufman HL, Russell J, Hamid O, Bhatia S, Terheyden P, D'Angelo SP, et al. Avelumab in patients with chemotherapy-refractory metastatic Merkel cell carcinoma: a multicentre, single-group, open-label, phase 2 trial. The Lancet Oncology. 2016;17(10):1374-85.

35. Lepone LM, Donahue RN, Farsaci B, Grenga I, Boyerinas B, Joschems C, et al. Evaluation of immune cell subsets of cancer patients treated with a fully human IgG1 anti-PD-L1 MAb (MSB0010718C) capable of mediating ADCC of human tumor cells. Cancer Res. 2015;75(15):1316.

36. Vandeveer AJ, Fallon JK, Tighe R, Sabzevari H, Schlom J, Greiner JW. Systemic Immunotherapy of Non-Muscle Invasive Mouse Bladder Cancer with Avelumab, an Anti-PD-L1 Immune Checkpoint Inhibitor. Cancer immunology research. 2016;4(5):452-62.

37. Iacovelli R, Nolè F, Verri E, Renne G, Paglino C, Santoni M, et al. Prognostic Role of PD-L1 Expression in Renal Cell Carcinoma. A Systematic Review and Meta-Analysis. Targeted Oncology. 2016;11(2):143-8.

38. Wu P, Wu D, Li L, Chai Y, Huang J. PD-L1 and Survival in Solid Tumors: A Meta-Analysis. PloS one. 2015;10(6):e0131403.

39. Gulley JL, Rajan A, Spigel DR, Iannotti N, Chandler J, Wong DJL, et al. Avelumab for patients with previously treated metastatic or recurrent non-small-cell lung cancer (JAVELIN Solid Tumor): dose-expansion cohort of a multicentre, open-label, phase 1b trial. The Lancet Oncology. 2017;18(5):599-610.

40. Kantekure K, Yang Y, Raghunath P, Schaffer A, Woetmann A, Zhang Q, et al. Expression patterns of the immunosuppressive proteins PD-1/CD279 and PD-L1/CD274 at different stages of cutaneous T-cell lymphoma/mycosis fungoides. The American Journal of dermatopathology. 2012;34(1):126-8.

41. Wilcox RA, Feldman AL, Wada DA, Yang ZZ, Comfere NI, Dong H, et al. B7-H1 (PD-L1, CD274) suppresses host immunity in T-cell lymphoproliferative disorders. Blood. 2009;114(10):2149-58.

42. Vranic S, Ghosh N, Kimbrough J, Bilalovic N, Bender R, Arguello D, et al. PD-L1 Status in Refractory Lymphomas. PloS one. 2016;11(11):e0166266.

43. Atsaves V, Tsesmetzis N, Chioureas D, Kis L, Leventaki V, Drakos E, et al. PD-L1 is commonly expressed and transcriptionally regulated by STAT3 and MYC in ALK-negative anaplastic large-cell lymphoma. Leukemia. 2017;31:1633.

44. Choi J, Goh G, Walradt T, Hong BS, Bunick CG, Chen K, et al. Genomic landscape of cutaneous T cell lymphoma. Nature genetics. 2015;47(9):1011-9.

45. da Silva Almeida AC, Abate F, Khiabanian H, Martinez-Escala E, Guitart J, Tensen CP, et al. The mutational landscape of cutaneous T cell lymphoma and Sezary syndrome. Nature genetics. 2015;47(12):1465-70.

46. Kataoka K, Nagata Y, Kitanaka A, Shiraishi Y, Shimamura T, Yasunaga J, et al. Integrated molecular analysis of adult T cell leukemia/lymphoma. Nature genetics. 2015;47(11):1304-15.

47. Vaque JP, Gomez-Lopez G, Monsalvez V, Varela I, Martinez N, Perez C, et al. PLCG1 mutations in cutaneous T-cell lymphomas. Blood. 2014;123(13):2034-43.

48. Wang L, Ni X, Covington KR, Yang BY, Shiu J, Zhang X, et al. Genomic profiling of Sezary syndrome identifies alterations of key T cell signaling and differentiation genes. Nature genetics. 2015;47(12):1426-34.

49. Jochems C, Tritsch SR, Pellom ST, Su Z, Soon-Shiong P, Wong HC, et al. Analyses of functions of an anti-PD-L1/TGFbetaR2 bispecific fusion protein (M7824). Oncotarget. 2017;8(43):75217-31.

50. Anand K, Ensor J, Pingali SR, Hwu P, Duvic M, Chiang S, et al. T-cell lymphoma secondary to checkpoint inhibitor therapy. J ImmunoTher Cancer. 2020;8(1):e000104.

51. Ratner L, Waldmann TA, Janakiram M, Brammer JE. Rapid Progression of Adult T-Cell Leukemia–Lymphoma after PD-1 Inhibitor Therapy. New England Journal of Medicine. 2018;378(20):1947-8.

52. Younes A, Hilden P, Coiffier B, Hagenbeek A, Salles G, Wilson W, et al. International Working Group consensus response evaluation criteria in lymphoma (RECIL 2017). Annals of Oncology. 2017;28(7):1436-47.

53. Olsen EA, Whittaker S, Kim YH, Duvic M, Prince HM, Lessin SR, et al. Clinical End Points and Response Criteria in Mycosis Fungoides and Sézary Syndrome: A Consensus Statement of the International Society for Cutaneous Lymphomas, the United States Cutaneous Lymphoma Consortium, and the Cutaneous Lymphoma Task Force of the European Organisation for Research and Treatment of Cancer. Journal of Clinical Oncology. 2011;29(18):2598-607.

54. Agresti A, Coull BA. Approximate Is Better than "Exact" for Interval Estimation of Binomial Proportions. The American Statistician. 1998;52(2):119-26.

55. Donahue RN, Lepone LM, Grenga I, Jochems C, Fantini M, Madan RA, et al. Analyses of the peripheral immunome following multiple administrations of avelumab, a human IgG1 anti-PD-L1 monoclonal antibody. Journal for ImmunoTherapy of Cancer. 2017;5(1):20.

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: GLOBAL RESPONSE SCORE AND DEFINITIONS OF RESPONSE IN SKIN, LYMPH NODES, VISCERA, AND BLOOD

Global Response Score					
Global Score	Definition	Skin	Nodes	Blood	Viscera
CR	Complete disappearance of all clinical evidence of disease	CR	All categories have CR/NI		
PR	Regression of measurable disease	CR	All categories do not have a CR/NI and no category has a PD		
		PR	No category has a PD and if any category involved at baseline at least one has a CR or PR		
SD	Failure to attain CR, PR, or PD representative of all disease	PR	No category has a PD and if any category involved at baseline, no CR or PR in any		
		SD	CR/NI, PR, SD in any category and no category has a PD		
PD	Progressive disease	PD in any category			
Relapse	Recurrence of disease in prior CR	Relapse in any category			
Abbreviations: CR, complete response; NI, noninvolved; PR, partial response; PD, progressive disease; SD, stable disease.					

Response in Skin	
Response	Definition
Complete response	100% clearance of skin lesions
Partial response	50%-99% clearance of skin disease from baseline without new tumors (T3) in patients with T1, T2 or T4 only skin disease
Stable disease	<25% increase to <50% clearance in skin disease from baseline without new tumors (T3) in patients with T1, T2, or T4 only skin disease
Progressive disease	≥25% increase in skin disease from baseline or New tumors (T3) in patients with T1, T2, or T4 only skin disease or Loss of response: in those with complete or partial response, increase of skin score of greater than the sum of nadir plus 50% baseline score
Relapse	Any disease recurrence in those with complete response
Notes: Percentages refer to mSWAT score. A biopsy of normal appearing skin is unnecessary to assign a complete response. However, a skin biopsy should be performed of a representative area of the skin if there is any question of residual disease (persistent erythema or pigmentary change) where otherwise a complete response would exist. If histologic features are suspicious or suggestive of mycosis fungoides/Sézary syndrome, the response should be considered a partial response only.	

Response in Lymph Nodes	
Response	Definition
CR	All lymph nodes are now ⩽1.5 cm in greatest transverse (long axis) diameter by method used to assess lymph nodes at baseline or biopsy negative for lymphoma; in addition, lymph nodes that were N3 classification and ⩽1.5 cm in their long axis and >1 cm in their short axis at baseline, must now be ⩽1 cm in their short axis or biopsy negative for lymphoma
PR	Cumulative reduction ⩾50% of the SPD of each abnormal lymph node at baseline and no new lymph node >1.5 cm in the diameter of the long axis or >1.0 cm in the diameter of the short axis if the long axis is 1-1.5 cm diameter
SD	Fails to attain the criteria for CR, PR, and PD
PD	≥50% increase in SPD from baseline of lymph nodes OR Any new node >1.5cm in the long axis or >1cm in the short axis if 1-1.5 cm in the long axis that is proven to be N3 histologically OR Loss of response: >50% increase from nadir in SPD of lymph nodes in those with PR (whichever occurs first)
Relapse	Any new lymph node >1.5 cm in the long axis in those with CR proven to be N3 histologically
Abbreviations: CR, complete response; PR, partial response; SPD, sum of the maximum linear dimension (major axis) × longest perpendicular dimension (minor axis); SD, stable disease; PD, progressive disease.	

Response in Viscera	
Response	Definition
CR	Liver or spleen or any organ considered involved at baseline should not be enlarged on physical exam and should be considered normal by imaging; no nodules should be present on imaging of liver or spleen; any post treatment mass must be determined by biopsy to be negative for lymphoma
PR	≥50% regression in any splenic or liver nodules, or in measurable disease (SPD) in any organs abnormal at baseline; no increase in size of liver or spleen and no new sites of involvement
SD	Fails to attain the criteria for CR, PR, and PD
PD	>50% increase in size (SPD) of any organs involved at baseline OR New organ involvement OR Loss of response: >50% increase from nadir in the size (SPD) of any previous organ involvement in those with PR (whichever occurs first)
Relapse	New organ involvement in those with CR
Abbreviations: CR, complete response; PR, partial response; SPD, sum of the maximum linear dimension (major axis) × longest perpendicular dimension (minor axis); SD, stable disease; PD, progressive disease.	

Response in Blood*	
Response	Definition
CR†	B_0
PR‡	≥50% decrease in quantitative measurements of blood tumor burden from baseline in those with high tumor burden at baseline (B_2)
SD	Fails to attain the criteria for CR, PR, and PD
PD§	B_0 to B_2 or > 50% increase from baseline and at least 5,000 neoplastic cells/μL or Loss of response: in those with PR who were originally B2 at baseline, > 50% increase from nadir and at least 5,000 neoplastic cells/μL
Relapse	Increase of neoplastic blood lymphocytes to ⩾ B_1 in those with CR

Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.
* As determined by absolute number of neoplastic cells/μL
† If a bone marrow biopsy was performed at baseline and determined to unequivocally be indicative of lymphomatous involvement, then to confirm a global CR where blood assessment now meets criteria for B_0, a repeat bone marrow biopsy must show no residual disease or the response should be considered a PR only.
‡ There is no PR in those with B_1 disease at baseline as the difference within the range of neoplastic cells that define B1 is not considered significant and should not affect determination of global objective response.
§ Whichever occurs first

16.4 APPENDIX D: 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), should 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 (1 mcg/kg), Dose Level 2 (2 mcg/kg), Dose Level 3 (3 mcg/kg), and Dose Level 4 (4 mcg/kg)

To prepare an IL-15 dose for Dose Level 1 (1 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 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**

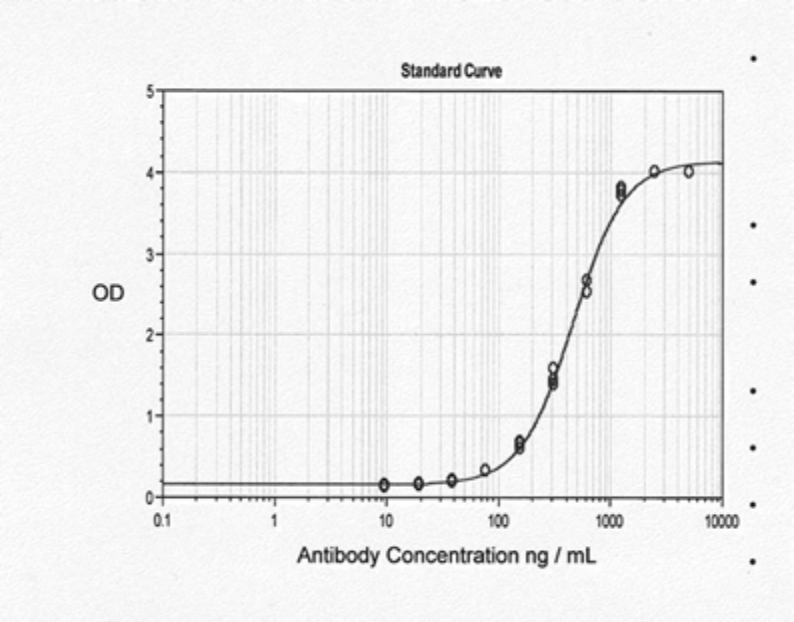
Diluent volume =
_____ mL (Total infusion volume) - _____ mL (IL-15 volume) = _____ mL

Patient's weight	IL-15 volume (490 mcg/ml)				Diluent volume				Total infusion volume (1 mcg/ml)			
	DL1	DL2	DL3	DL4	DL1	DL2	DL3	DL4	DL1	DL2	DL3	DL4
60 kg	0.14	0.27	0.39	0.51	69.86	129.73	189.61	249.49	70 ml	130 ml	190 ml	250 ml
75 kg	0.17	0.33	0.48	0.63	84.83	159.67	234.52	309.37	85 ml	160 ml	235 ml	310 ml
90 kg	0.20	0.39	0.57	0.76	99.80	189.61	279.43	369.24	100 ml	190 ml	280 ml	370 ml
105 kg	0.23	0.45	0.66	0.88	114.77	219.55	324.32	429.12	115 ml	220 ml	325 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

16.5 APPENDIX E: 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.