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Title: Phase 1 Study of Recombinant Human IL-15 (rhIL-15) and Mogamulizumab for Patients with Refractory or Relapsed Adult T-Cell Leukemia and Mycosis Fungoides/Sézary Syndrome

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Investigational Agents:

Drug Name:	Recombinant human IL-15 (rhIL-15; NSC #745101)
IND Number:	140549
Sponsor:	Center for Cancer Research, NCI
Manufacturer:	Biopharmaceutical Development Program (BDP)/Leidos Biomedical Research, Inc. under contract with DCTD, NCI

Commercial Agents: Mogamulizumab (Poteligeo®)

PRÉCIS

Background:

- Advanced mycosis fungoides, its leukemic form Sézary syndrome (MF/SS), and adult T-cell leukemia/lymphoma (ATLL) are all aggressive mature T-cell malignancies which are considered incurable without an allogeneic stem cell transplant.
- Mogamulizumab is a defucosylated monoclonal antibody directed towards CCR4, a chemokine receptor expressed by the majority of MS/SS and ATLL cells. It is approved by the United States Food and Drug Administration for treatment of relapsed MF/SS, and is recommended by the National Comprehensive Cancer Network for treatment of ATLL.
- Defucosylation of mogamulizumab is thought to enhance its capacity for antibody-dependent cell cytotoxicity (ADCC), which is mediated by natural killer (NK) cells and macrophages.
- 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 I trials in cancer patients.
- Concomitant administration of rhIL-15 with mogamulizumab may further enhance the ADCC capacity of the antibody and result in improved efficacy for patients with CCR4-expressing cancers.

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) mogamulizumab treatment

Eligibility:

- Age $\geq$ 18 years of age
- ECOG performance status of $\leq$ 1
- Histologically or cytologically confirmed mycosis fungoides/Sézary syndrome or adult T-cell leukemia/lymphoma relapsed after or refractory to at least one line of systemic treatment.
- Adequate organ and marrow function

Design:

- Open-label, single-center, non-randomized phase I study
- Standard “3 + 3” design will be used to determine the MTD of dose-escalated rhIL-15 with fixed dose of mogamulizumab, with an expansion cohort at the MTD
- Maximum 6 cycles (28-day cycles) of combination therapy
- To explore all dose levels, including further evaluation in a dose expansion cohort, and to account for unevaluable patients the accrual ceiling will be set at 20 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; a 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) mogamulizumab treatment

1.1.2 Secondary Objective(s)

- Determine the efficacy of combined CIV rhIL-15 and mogamulizumab treatment in patients with ATLL and MF/SS by assessing the overall response rate (ORR), time-to-progression (TTP), and progression-free survival (PFS).
- Determine the effect of CCR4 mutation status (mutated versus wild type) and presenting diagnosis (MF/SS versus ATLL, MF versus SS, acute and chronic versus lymphoma subtype ATLL) on ORR, TTP, and PFS
- Define the effects of rhIL-15 on the antibody-dependent cell-mediated cytotoxicity (ADCC) mediated by mogamulizumab, using ex-vivo peripheral blood mononuclear cells (PBMCs)

1.1.3 Exploratory Objective(s)

- Better understand the *in vivo* biologic effects of mogamulizumab and rhIL-15 treatment by:
    - analyzing changes in peripheral blood lymphocyte subsets
    - examining treatment-related changes in tumor deposits by immunohistochemical and molecular analysis of core biopsies obtained before and during treatment.
- Assess circulating tumor DNA as a prognostic and predictive biomarker in MF/SS and ATLL.

1.2 BACKGROUND AND RATIONALE

1.2.1 Adult T-cell leukemia/lymphoma (ATLL)

ATLL is an aggressive T-cell lymphoproliferative disorder characterized by the presence of malignant CD4/CD25/CCR4-expressing T cells in the peripheral blood, lymphoid tissues, and other organs. Epidemiological studies demonstrated clear association of the disease with the presence of the retrovirus human T-cell lymphotrophic virus-1 (HTLV-1). ATLL cells exhibit immunophenotypic characteristics of mature T-regulatory cells, with surface expression of $CD3^{dim}$, CD4, and CD25, and loss of CD7. There are four clinical subtypes of ATL (**Table 1**), with median overall survival (OS) ranging from 72 months for chronic/smoldering, 10.2 months for lymphomatous, and only 4.1 months for acute subtype in a cohort of 195 patients of predominantly Caribbean origin treated with modern therapies between 2000 and 2016.(1)

Table 1: **Clinical subtypes of adult T-cell leukemia/lymphoma**

Subtype	Clinical features	Lymphocyte count	Associated biochemical abnormalities
Smoldering	Skin and pulmonary lesions No LAD or organ involvement	≥ 5% abnormal T cells Normal ALC (< 4 x 10^9/L)	Calcium, LDH < 1.5 × ULN
Chronic	Skin and lung involvement, no CNS, bone, GI tract involvement, no ascites or pleural effusions	ALC > 4 x 10^9/L T cells > 3 x 10^9/L	LDH elevated but < 2 × ULN Calcium normal
Lymphoma	Biopsy-proven LAD	Normal ALC, ≤ 1% abnormal circulating T-cells	
Acute	Tumor lesions	Leukemia	Not required for diagnosis

ALC, absolute lymphocyte count; LDH, lactate dehydrogenase; ULN, upper limit of normal; LAD, lymphadenopathy; CNS, central nervous system. (adapted from Shimoyama et al.(2)

1.2.1.1 Treatment of ATLL

There are no curative therapeutic options for patients with ATLL outside of early allogeneic stem cell transplantation, ideally immediately after achieving a complete response to first-line chemotherapy.(3) Prognosis of ATLL relapsed or refractory to front-line therapy is dismal(4), and experience with the standard combination chemotherapeutic regimens known to be useful in the treatment of the more common aggressive B-cell non-Hodgkin lymphomas or acute lymphoblastic leukemia has been disappointing. In North America, the majority of patients with the three more aggressive categories of ATLL (severe chronic, acute, and lymphoma subtype) are still treated with CHOP-based regimens (cyclophosphamide, Adriamycin, vincristine and prednisone) with or without interferon and zidovudine.(5) In countries where ranimustine and vindesine are available, and which have the infrastructure for a more intensive chemotherapy regimen, the LSG15 protocol (VCAP-AMP-VECP) is an option shown to be superior to biweekly CHOP in a phase III trial (complete response [CR] rate 40% v. 25%, 3-year OS 24% v. 13%).(6) A meta-analysis showed that the addition of interferon and zidovudine to first-line therapy improved OS of patients with acute, chronic, and smoldering subtypes(7), but there was a lack of efficacy in patients with relapsed disease.

There are no US FDA-approved drugs for relapsed/refractory ATLL, and no randomized phase III trials have been conducted in this patient population. Mogamulizumab (KW-0761), a monoclonal antibody targeting CCR4, is approved in Japan for treatment of CCR4-positive ATLL. In a phase II trial of 27 Japanese patients with relapsed ATLL, overall response rate (ORR) was 50% (95% CI 30% to 70%), median progression-free survival (PFS) was 5.2 months, and median OS 13.7 months.(8) An international randomized phase II study of mogamulizumab versus investigator-choice chemotherapy in 71 patients from the US, Europe, and Latin America with aggressive relapsed/refractory ATLL showed confirmed ORR (response lasting ≥8 weeks) to be 11% versus 0%, and best ORR 28% versus 8% (*in press*).

Lymphoid Malignancies Branch (LYMB) conducted a phase II trial of alemtuzumab (Campath), an anti-CD52 monoclonal antibody, in 29 patients with relapsed chronic, acute, and lymphomatous

subtypes of ATLL. ORR was 52% (95% CI 32% to 70%), but median duration of response was only 1.4 months, with median PFS and OS of 2.0 and 5.9 months respectively.(9)

Treatment with Lenalidomide, given to 26 patients in a multicenter phase II trial, resulted in an ORR of 42% (95% CI 23% to 63%), including four CRs and one unconfirmed CR.(10) Median PFS and OS were 3.8 and 20.3 months respectively. Phase II trials of single-agent cladribine, arsenic trioxide with alpha interferon, and bortezomib have all shown modest results (ORR 4% to 7%) with significant toxicity.(11-13)

1.2.2 Mycosis fungoides/Sézary syndrome (MF/SS)

Cutaneous T-cell lymphomas are a diverse group of non-Hodgkin lymphomas characterized by primary cutaneous infiltration of malignant T cells. Mycosis fungoides (MF), the most common type of CTCL, arises from accumulation of aberrant effector/resident memory $CD4^+$ T-cells in skin lesions, while malignant clones in Sézary syndrome (SS), the erythrodermic and leukemic form of CTCL, are thought to arise de novo as an expansion of central memory T-cells. Although very early stage MF patients have an indolent course with median OS of 15-35 years, those with ≥ stage IIB and SS patients have compromised survival (median OS of 4.7 years for stage IIB-IIIA, 2.1-3.8 years for stage IIIB-IVA, and 1.4 years for stage IVB).(14)

1.2.2.1 Treatment of MF/SS

Other than allogeneic hematopoietic stem cell transplantation(15), no treatment for MF/SS has been shown to be curative, and advanced disease can become refractory, leading to serious clinical complications.(14) Chemotherapy, including CHOP-based regimens, has high response rates (50-88%), but duration of response of <6 months and high toxicity.(14, 16, 17) There are five US FDA-approved drugs for relapsed/refractory MF/SS currently on the market: bexaroten, romidepsin, vorinostat, brentuximab vedotin, and the recently approved mogamulizumab. The sixth, anti-CD25 immunotoxin denileukin diftitox, was withdrawn by the manufacturer and is no longer available.

The RXR-selective retinoid bexaroten was given at two different dose levels to 94 patients with stage ≥IIB CTCL, of whom 31% had erythroderma and 10% had visceral involvement.(18) Only 16% of patients had ≥15% circulating Sézary cells, though 27% had the cells detectable. 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 SS had a response. The most common grade 3 or 4 AEs were hyperlipidemia (34- 45%) and pruritus (8-14%). One of 17 deaths was 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. 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%).(19)

Another HDAC inhibitor, romidepsin, was investigated in two concurrent phase II trials which included a total of 167 patients, 130 of whom had stage ≥IIB disease.(20, 21) 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 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.

Results of a phase III trial of brenutixmab vedotin compared to methotrexate or bexaroten in CD30+ CTCL were reported as positive for improvement in global overall response lasting at least 4 months (ORR4), which was 56.3% vs. 12.5% after a median follow-up of 22.9 months.(22)

Finally, mogamulizumab has shown efficacy in patients with cutaneous T-cell lymphoma. In the phase I/II study, among the 38 evaluable patients the ORR was 36.8%; 47.1% in SS (n = 17) and 28.6% in MF (n = 21).(23) Eighteen of 19 (94.7%) patients with blood involvement had a response in blood, including 11 CRs. Efficacy of mogamulizumab was confirmed in a phase III randomized controlled trial which demonstrated a median 4.6-month improvement in PFS as compared to vorinostat (7.7 vs. 3.1 months).(24) Importantly, CCR4 expression was not required for treatment, though an exploratory analysis showed 97% (280 of 290) patients to be CCR4 positive, defined as having at least 10% infiltrating $CCR4^+$ lymphocytes on immunohistochemistry. No differences in response were seen in patients on the basis of skin CCR4 expression. Mogamulizumab was well-tolerated, with the majority of events Grade 1/2 that included nausea, chills, headache and infusion-related reactions.

1.2.3 Chemokine Receptor 4 (CCR4)

CCR4 is a chemokine receptor that has a critical role in immune cell trafficking. Expression of CCR4 on normal lymphocytes is modest, as it is found predominantly on T-regs and skin-homing memory T-cells that migrate toward the chemokines CCL17 and CCL22, which interact with the receptor CCR4. In contrast to the relative non-expression of CCR4 on normal lymphocytes, the leukemic cells in 90 percent of patients with ATLL cells express CCR4 on their surface.(25) Interestingly, the most frequent sites of ATLL involvement are lymph nodes and skin where dendritic cells, M2-phenotype macrophages, Langerhans cells, and cutaneous venules can produce CCL17 and/or CCL22. A number of studies have provided insights concerning the mechanisms underlying the expression of CCR4 on ATLL cells. In our own studies we discovered recurrent somatic mutations in CCR4 in 14 of 53 ATLL cell samples (26 percent) that consisted exclusively of nonsense or frameshift mutations that truncated the coding region at C329, Q330, or Y331 in the carboxyl terminus.(26) Due to the deletion of the carboxyl terminus the CCR4 expression was maintained on the ATLL cells rather than internalizing on the interaction with its cognate chemokine. Functionally, the CCR4 Q330 nonsense isoform was a gain-of-function because it increased cell migration towards CCR4 ligands CCL17 and CCL22. Furthermore, this mutant enhanced PI (3) kinase/AKT activation after receptor engagement by CCL22 and conferred a growth advantage in long-term *in vivo* cultures. Even in the absence of the mutations it has been demonstrated that HBZ encoded by HTLV-1 in ATLL cells acts on the promoter of CCR4 augmenting expression of this receptor. In MF/SS, CCR4 was detected by peripheral blood flow cytometry in 63% of patients(27), and by IHC of skin lesions in 97% (with positivity defined as ≥10% of infiltrating lymphoid cells).(24) Similarly to ATLL, genomic studies of patients with SS have described gain-of-function nonsense mutations Q330 and Y331, as well as a new nonsense mutation Y347, and two new frame shift mutations, C322fs and D341fs.(28) Taken together these findings implicate CCR4 expression in the pathogenesis of ATLL and MF/SS, and suggest that inhibition of CCR4 and its signaling may have therapeutic potential in these malignancies.

1.2.4 Mogamulizumab

As noted above, the CC chemokine receptor 4 is expressed in the malignant cells of 90% of patients with ATLL and 97% of patients with MF/SS, however, with the exception of Tregs, is minimally expressed on normal lymphocytes. Mogamulizumab (KW-0761) is a defucosylated humanized mAb with enhanced antibody cellular cytotoxicity (ADCC) that binds to CCR4.(29) Mogamulizumab is devoid of complement dependent cytotoxicity. The antibody has shown potent antitumor activity mediated by highly enhanced ADCC against primary ATLL cells both *in vitro* and *in vivo*.(30) The degree of mogamulizumab ADCC against primary ATLL cells in an autologous setting was mainly determined by the amount of effector natural killer (NK) cells present but not on the amount of targeted molecule CCR4 on the ATLL cell surface.(30) It is approved in Japan for treatment of CCR4-positive relapsed/refractory ATLL and MF/SS, and in the US for the treatment of any MF/SS after at least one prior systemic therapy.

In a post-marketing all-case survey conducted in Japan of patients with ATLL who received mogamulizumab, the overall response rate in the 308 patients treated with single-agent therapy was 57.7%.(31) Forty-two patients had received mogamulizumab after an allogeneic stem cell transplant. Grade 3 or 4 acute graft versus host disease (GVHD) occurred in 28.6% of these patients, all of whom received mogamulizumab within 90 days of transplant. Chronic GVHD occurred in 45% of patients who survived beyond 100 days after transplant. In a different analysis, patients with ATLL who carried any CCR4 gain-of-function mutation had superior response to mogamulizumab compared with wild-type CCR4 (5-year OS 72.2% vs. 26.2%), despite patients with mutated CCR4 doing worse compared to unmutated patients in historic controls. As hypothesized when CCR4 gain-of function mutations were first described(26), this was likely the effect of impaired CCR4 internalization upon ligand binding, resulting in increased CCR4 expression even in the presence of the ligand.

1.2.5 Interleukin-15

IL-15 is a 14-15 kDa member of the 4 alpha-helix bundle family of cytokines that acts through a heterotrimeric receptor involving IL-2/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).(32-36) IL-15 acts as a cell surface molecule as a 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. A number of studies in murine models suggested that IL-15 may prove to be of value in the therapy of 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.(33) When administered by CIV at 20 µg/day for 10 days it led to 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.(34) Subcutaneous injections at 20 µg/day for 10 days led to a 10-fold expansion in the number of circulating effector memory CD8 T-cells (**Figure 1**).(35)

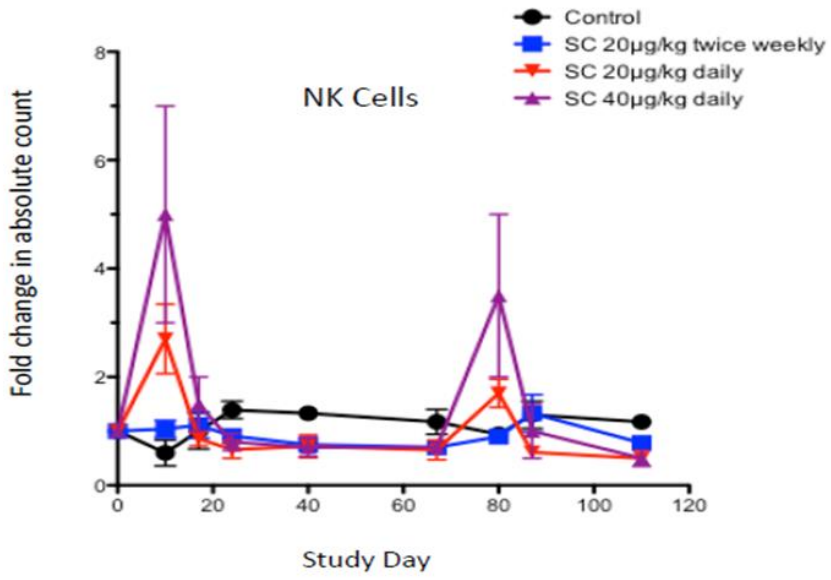


Figure 1. Fold-Increase in absolute NK cell counts in rhesus macaques

1.2.5.1 IL-15 in the Treatment of Patients with Metastatic Malignancy

Three clinical trials of rhIL15 have had their patient accrual completed with 19-29 patients each: one by bolus infusion over 30 minutes(37), one by subcutaneous (SC) administration(38), and the third by CIV of rhIL15 to patients with metastatic malignancy.(39) The MTD by bolus infusion was 0.3 mcg/kg/day, whereas the MTD with SC administration was 3 mcg/kg/day and by CIV was 2 mcg/kg/day.

In the phase I study of bolus infusions of recombinant Escherichia coli produced human IL-15, the MTD was determined to be 0.3 µg/kg/day for 12 days. At a dose of 3 µg/kg/day the patients developed fever and rigors and a reduction in blood pressure that were concurrent with a maximum of 50-fold elevations of circulating IL-6 and IFNγ concentrations. The bolus infusion of IL-15 at 3 µg/kg/day led to a 10-fold expansion of NK cells. When IL-15 was administered subcutaneously 5 days a week for 2 weeks at 3 mcg/kg/day there was a significant increase (mean 10.8 fold) in the number of circulating NK cells. Furthermore, when it was administered at 2 mcg/kg/day by continuous intravenous infusion there was an 8-fold increase in this number during the infusion. Following termination of the infusion there was a 38-fold increase in the number of NK cells and a 358-fold increase in the number of CD56bright NK cells (**Figure 2**A). A trial of IL-15 by CIV for 5 days has been initiated, and in the 11 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**B, **Table 2** and **Table 3**).

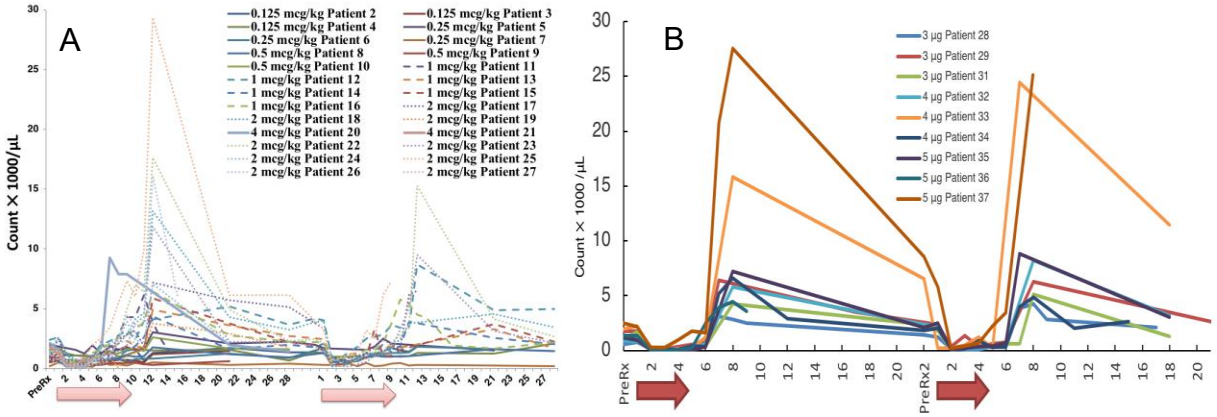


Figure 2: Increase in lymphocytes, predominantly NK cell count, during continuous infusion of rhIL-15.

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

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

Table 3: Lymphocyte subset changes observed with four rhIL-15 dosing regimens at the recommended dose.

Regimen	RP2D (mcg/kg)	Mean fold increase at RP2D		
		NK	CD56^{bright}	CD8 T
IVB	0.3	2.5		8
SC	2	10.8	37	3.3
CIV-10	2	31	400	3.3
CIV-5	4	42	Pending	4.8

RP2D: recommended phase 2 dose, IVB: intravenous bolus, SC: subcutaneous injection, CIV-10: 10-day continuous intravenous infusion, CIV-5: 5-day continuous intravenous infusion.

The best response has been stable disease. There have been no dose-limiting toxicities. Two patients (at 3 and 5 mcg/kg/day dose levels) did not complete cycle 1 for reasons unrelated to IL-15 and have completely recovered since. One patient at the 4 mcg/kg/day dose level developed bilateral arthritis which was thought to be septic and unrelated to IL-15, with mostly PMNs and some GPCs in the synovial fluid. Other AEs have been identical to what was seen in patients receiving 10-day infusion, though shorter in duration (**Table 4** and **Table 5**).

Table 4: Clinical adverse events possibly, probably, or definitely related to research (5-day CIV cohort) excluding single grade 1 events

Dose	3 µg/kg n=4				4 µg/kg n=3				5 µg/kg n=4			
CTC V4 Grade	1	2	3	4	1	2	3	4	1	2	3	4
Arthritis						1						
Bladder infection		1										
Chills	1	1				2				2		
Constipation	1								1			
Diarrhea	2				1				1	1		
Dizziness					2							
Dry mouth	1				2							
Dry skin						1						
Edema limbs	1	1										
Fatigue	1	1							2	1		
Fever	2	2			1	1			2	2		
Headache	1				1							
Hypotension		1				1			1			
Nausea	2				2				3			
Pulmonary edema		1										
Rash maculo-papular	2								2			
Vomiting	2				1				2			

Table 5: Laboratory abnormalities possibly, probably, or definitely related to research (5-day CIV cohort) excluding single grade 1 events

	3 µg/kg n=4				4 µg/kg n=3				5 µg/kg n=4			
CTC V4 Grade	1	2	3	4	1	2	3	4	1	2	3	4
Anemia			2			2			1	1	1	
ALT increased	1	1			1	1			3			
AST increased		2			2				4			
Alkaline phosphatase		1			1		1		2	1		
Hyperbilirubinemia	1	1				1			1		1	
Hypoalbuminemia		2			1	1			2	2		
Creatinine increased					1				1	2		
Hyperglycemia										1		
Hypernatremia	2										1	
Hyponatremia	1		1		2				3			
Hypocalcemia	1				1				4			
Hypokalemia	2	1							1		2	
Hypomagnesemia					1				3			
Hypophosphatemia		1	2			2				1	2	
Lymphocytosis				2				2			1	2
Lymphopenia		1				1	1			2	1	1
Neutropenia	1				1		1			1		
Thrombocytopenia		2			2				1	1		
Leucopenia		2				1	1		1	1	1	

1.2.5.2 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 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.(40) Wild-type CD56 and BL/6 mice were inoculated intravenously with EL4-CD20 cells, a mouse lymphoma line transfected with human CD20 and 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 times 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. 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), so 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 3**). In a parallel preclinical trial, the Waldmann Group administered a combination therapy of alemtuzumab with rhIL-15 in the MET-I bearing xenograft model in wild-type SCID/NOD mice (**Figure 4**). Again, there was an augmentation of survival of the combination of IL-15 with alemtuzumab compared to either element alone.

In summary, clinical trials in humans indicate that IL-15 administered by CIV is well tolerated and is associated with an increase in the number of NK cells. Furthermore, studies combining monoclonal antibodies with IL-15 in syngeneic and xenogeneic murine tumor models provide scientific support for the combination of antitumor monoclonal antibodies with IL-15 in patients with chronic and acute lymphoma forms of ATLL. All previous trials in patients with acute ATLL have been closed for patient accrual.

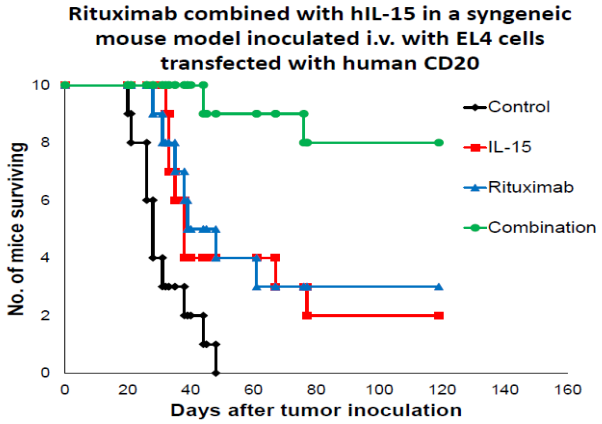


Figure 3:The effect of Rituximab and human IL-15 treatment of CD20+ Lymphoma

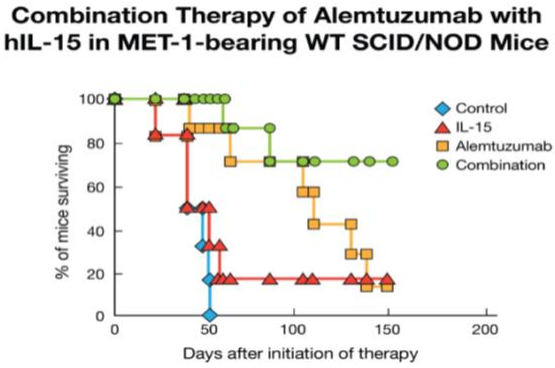


Figure 4:The effect of Alemtuzumab and human IL-15 treatment of ATL cell line MET-1

2 ELIGIBILITY ASSESSMENT AND ENROLLMENT

2.1 ELIGIBILITY CRITERIA

2.1.1 Inclusion Criteria

2.1.1.1 Patients must have one of the following histologically or cytologically proven relapsed and/or refractory to at least one line of systemic treatment, T-cell malignancies confirmed by the Laboratory of Pathology, NCI: mycosis fungoides/Sézary syndrome, or adult T-cell leukemia (chronic, acute, or lymphoma subtype by Shimoyama criteria, see **Table 1**)

2.1.1.2 Patients with CD30+ MF/SS 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 mogamulizumab 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 Patients must have normal organ and marrow function as defined below:

Absolute neutrophil count	≥ 1,000/mcL
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.

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 6 months after completion of rhIL-15 and mogamulizumab 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 other T-cell leukemias/lymphomas not specified in the inclusion criteria

2.1.2.2 Anti-cancer treatment within 2 weeks of the first dose of rhIL-15 and mogamulizumab (4 weeks for anti-cancer monoclonal antibody or investigational agents, 6 weeks for donor lymphocyte infusion, 100 days for allogeneic stem cell transplant)

2.1.2.3 Systemic treatment for acute or chronic graft versus host disease (GVHD) within 12 weeks of the first dose of rhIL-15 and mogamulizumab

2.1.2.4 Cohort 1 (Dose Escalation) only: history of grade 3/4 GVHD, or active grade 1/2 GVHD regardless of treatment

2.1.2.5 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

2.1.2.6 Patients who are receiving any other investigational agents

2.1.2.7 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)

2.1.2.8 Patients with previous malignant disease other than the target malignancy within the last 3 years with the exception of basal or squamous cell carcinoma of the skin or cervical carcinoma in situ

2.1.2.9 Cohort 1 (Dose Escalation) only: Active or history of any autoimmune disease thought to be unrelated to their malignancy; for Cohort 2 (Dose Expansion), patients with history of autoimmune disease who are not on active immunosuppressive therapy per Section 2.1.2.7 are eligible.

2.1.2.10 Patients with asthma requiring chronic inhaled or oral corticosteroids, or 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

2.1.2.11 Patients with active bacterial infections, documented HIV infection or positive HIV 1/2 antibodies at screening, PCR evidence for active or chronic hepatitis B or hepatitis C, or positive screening HBV/HCV serology without documentation of successful curative treatment (see Section **12.1** for IL-15 administration in HIV positive patients)

2.1.2.12 Presence of uncontrolled intercurrent illnesses including but not limited to ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, cognitive impairment, active substance abuse, or psychiatric illness/social

situations that in the view of the Investigator would preclude safe treatment and 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. Because there is no significant preclinical information regarding the risks to a fetus or a newborn infant, all pregnant or breastfeeding woman will be excluded from participation in this trial

2.1.2.14 History of allergic reactions attributed to compounds of similar chemical or biologic composition to rhIL-15 or mogamulizumab, unless felt to be in the best interests of the patient in the opinion of the investigator

2.1.2.15 Patients who received a live vaccine within 30 days of planned start of study therapy. 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

2.1.3 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. This study will be posted on NIH websites: http://ccr.cancer.gov/Lymphoid-Malignancies-Branch and http://ClinicalTrials.gov, on NIH social media forums (Lymphoid Malignancy Branch and NIH social media accounts).

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, including medical history, physical evaluations, 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.

If felt to be possible candidates after review of the above and after subjects sign a research consent for screening, they will undergo the evaluations described in Section **2.2.2**.

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

The following screening activities will be performed only after the subject has signed the consent for study 01-C-0129 on which screening activities will be performed.

Assessments and procedures to confirm study eligibility should be completed within 28 days prior to registration (unless otherwise noted). Assessments performed at outside facilities or on another NIH protocol within the timeframes below may also be used to determine eligibility once

a patient has signed the consent. See also the Study Calendar provided in Section **3.7**. 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 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 due to elevated total bilirubin, at discretion of the lab) 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
- Coagulation panel, including: PT/INR and a PTT
- Thyroid function tests (thyroid stimulating hormone (TSH), with free thyroxine (T4) if TSH is abnormal)
- 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. For individuals with positive hepatitis C antibody and history of curative treatment, HCV DNA PCR will be performed to confirm the resolution of 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 (TTE)

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 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently assigned to the study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

2.3.2 Treatment Assignment and Randomization/Stratification Procedures

2.3.2.1 Cohorts

Number	Name	Description
1	Mature T-cell malignancies: Dose Escalation	Relapsed/refractory mycosis fungoides/Sézary syndrome, adult T-cell leukemia/lymphoma acute, chronic, and lymphoma subtype (up to 12 evaluable patients)
2	Mature T-cell malignancies: Dose Expansion	Relapsed/refractory mycosis fungoides/Sézary syndrome, adult T-cell leukemia/lymphoma acute, chronic, and lymphoma subtype (up to 9 additional evaluable patients, 12 total evaluable at the MTD)

2.3.2.2 Arms

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

Number	Name	Description
2	Experimental Treatment: Dose Expansion	IL-15 by CIV infusion at the MTD on days 1-5 of cycles 1-6 with mogamulizumab at 1 mg/kg on days 1, 8, 15, and 22 of cycle 1 and days 1 and 15 of cycles 2-6

2.3.2.3 Randomization and Assignment

Treatments 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 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 to measure CrCl if serum creatinine >1.5mg/dl)
  - Others: LDH, Uric acid, Total protein
  - Serum Lipase and Amylase
  - 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 free thyroxine if TSH is abnormal
  - Urinalysis (with microscopic examination if abnormal)
  - HLA typing (A, B, C, DR, DQ)
  - Soluble IL-2Rα

- 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 **5.1** for additional information. The following sample types will be collected for correlative research studies:

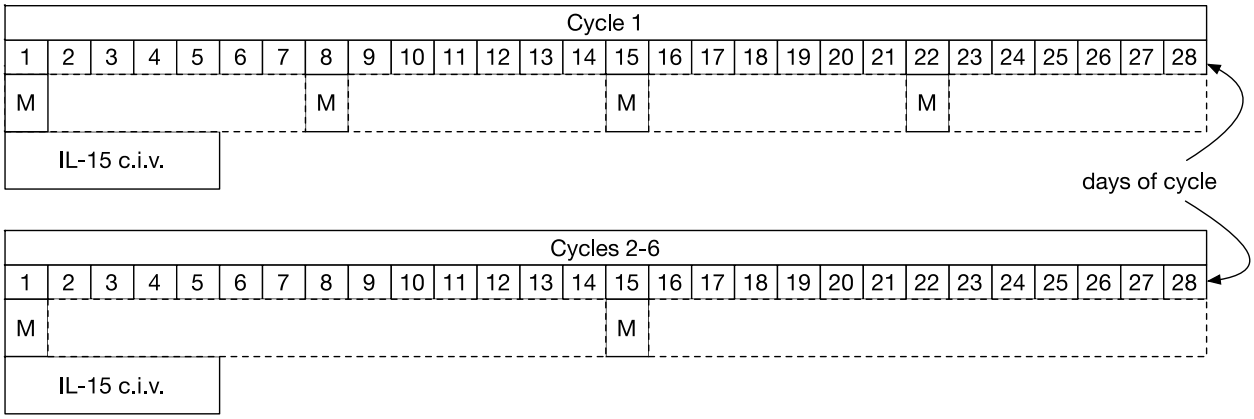
- Required:
  - Blood samples for lymphocyte subset testing and circulating tumor DNA
  - Blood, buccal swab, or saliva for germline DNA
  - Tumor Tissue (archival or fresh)
- Optional:
  - Blood samples for ADCC of mogamulizumab, tissue immune cell subset comparison (as outlined in Section **5.2**)
  - 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/refractory MF/SS or ATLL, IL-15 will be administered by continuous intravenous infusion in a dose-escalation 3 + 3 system with a starting dose of 2 mcg/kg/day and a second dose level of 4 mcg/kg/day on days 1-5 of each of six cycles. Mogamulizumab will be

administered IV over at least 1 hour at a dose of 1 mg/kg on days 1, 8, 15 and 22 of cycle 1, and days 1 and 15 of each subsequent 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 mogamulizumab 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.
- Grade 3 or 4 neutropenia without clinical signs of infection grade 2 or above.
- Grade 3 or 4 thrombocytopenia lasting fewer than 5 days and not associated with bleeding or purpura.
- 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.
- Non-sustained (< 7 days) grade 3 liver function test (ATL, AST, alkaline phosphatase, total or direct bilirubin) abnormalities 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.
- Grade 3 rash (maculo-papular, acneiform, or urticaria); if the rate of grade 3 rashes exceeds the expected rate (10% per mogamulizumab package insert) this will be reported as an unanticipated problem.
- First grade 3 infusion reaction associated with mogamulizumab administration (occurring within 24 hours of the dose).

Management and dose modifications associated with the above adverse events are outlined in Section **3.3**. If a DLT is possibly, probably, or definitely related to IL-15 and unrelated or

unlikely to be related to mogamulizumab, patient may continue treatment with mogamulizumab alone if PI or designate deems it to be in the patient's best interest. Any DLT at least possibly related to mogamulizumab will lead to permanent discontinuation of protocol therapy regardless of attribution to IL-15. The same management will apply to an occurrence of any DLT-defining toxicity after the first 28 days of treatment; however, that toxicity 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 6**). Dose escalation will follow the following guidelines (**Table 7**). 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 6: IL-15 Dose Escalation Schedule

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

Table 7: 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.
≥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 Section **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 8** below for description of drug regimen.

Table 8: 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
Mogamulizumab	Premedicate with acetaminophen and an antihistamine*	1 mg/kg in **** mL 0.9% Sodium Chloride for Injection	IV over 1 hour	Days 1, 8, 15 and 22 of Cycle 1 and Days 1 and 15 of Cycles 2-6

* Mandatory for the first infusion; subsequently based on clinical judgement
** Doses as appropriate for assigned dose level
*** Infusion volume of rhIL-15 per calculation in **APPENDIX D**
**** Infusion volume of mogamulizumab titrated to a final concentration of the diluted solution between 0.1 mg/mL and 3.0 mg/mL

For a full detailed product description and administration guidelines, see Section **14**. Infusions will be done via midline catheter. 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 as first line, and ibuprofen 400 or 600mg orally, depending on reactions with acetaminophen as premedication.

3.2.2 Prophylactic and supportive care for mogamulizumab

In order to mitigate infusion related reactions, a premedication with an antihistamine and with acetaminophen 30 to 60 minutes prior to the first infusion of mogamulizumab is mandatory (e.g., 25-50 mg diphenhydramine and 500-650 mg acetaminophen IV or orally). Premedication should be administered for subsequent mogamulizumab 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 mogamulizumab for potential infusion-related reactions.

3.2.4 Delays in Dosing

During the first treatment cycle, mogamulizumab should be administered beginning on Day 1 and within +/- 1 day of the other scheduled visits (i.e., Days 8, 15 and 22). For subsequent cycles, mogamulizumab should be administered within +/- 2 days of the scheduled visits.

3.3 DOSE MODIFICATIONS

3.3.1 rhIL-15-specific Adverse Events

Please refer to the Comprehensive Adverse Event and Potential Risk list (CAEPR) for rhIL-15 presented in Section **14.1.2**.

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.

3.3.2 Mogamulizumab-specific Adverse Events

3.3.2.1 Treatment modifications for symptoms of infusion-related reactions

Table 9: Treatment modifications for infusion-related reactions

NCI-CTCAE Grade	Treatment Modification for Mogamulizumab
Grade 1-3 – mild, moderate, or severe Grade 1: Mild transient reaction; infusion interruption not indicated; intervention not indicated. Grade 2: Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (for example, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 h. 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.	Temporarily interrupt the infusion of mogamulizumab and treat symptoms. Reduce the infusion rate by at least 50% when restarting the infusion after symptoms resolve. If reaction recurs and is unmanageable, discontinue infusion.
Grade 4 –life-threatening Life-threatening consequences; urgent intervention indicated.	Stop mogamulizumab infusion immediately and disconnect infusion tubing from the subject. Subjects have to be withdrawn immediately from study treatment and must not receive any further mogamulizumab treatment.
NOTE: If mogamulizumab 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	

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 dermatologic toxicity

Table 10: Treatment Modifications for Dermatological AEs

Dermatological irAEs		
Rash	**Initial Management**	**Resuming protocol treatment**
Grade 1 Covering <10% of body surface area	Continue protocol therapy Consider topical steroids	N/A
Grade 2 to 3 Covering >10% of body surface area	Hold protocol therapy Administer topical steroids for at least 2 weeks	Rash improves to Grade ≤1
Grade 4 Life-threatening consequences; Stevens-Jonson syndrome (SJS) or	Hold protocol therapy for suspected SJS/TEN Permanently discontinue protocol therapy if SJS/TEN has been	SJS/TEN has been excluded and the rash improves to Grade ≤1

Dermatological irAEs		
Rash	**Initial Management**	**Resuming protocol treatment**
toxic epidermal necrolysis (TEN)	confirmed or if there are life-threatening consequences	

3.4 STUDY INTERVENTION COMPLIANCE

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

3.5 ON STUDY EVALUATIONS

Prior to mogamulizumab administration (Days 1, 8, 15 and 22 of cycle 1 and days 1 and 15 of cycles 2-6), 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 mogamulizumab will continue for six cycles or until disease progression, unacceptable treatment-related toxicity or other reasons outlined in Section **3.9.1**.

Refer to the Study Calendars (Section **3.7**) for a complete list of procedures to be performed at each scheduled study visit. See also Section **5.1** for all samples to be collected for correlative research. During treatment, it is expected that all laboratory and clinical assessments be conducted at the NIH (including post-treatment imaging evaluations); results from outside NIH will only be accepted at the discretion of the investigator.

3.6 POST-TREATMENT EVALUATIONS

Post treatment evaluations (i.e., End of Treatment Visit) will be performed approximately 30 days after the last dose of protocol treatment. If a subject initiates a new anti-cancer therapy within 30 days after the last dose of trial treatment, the 30-day safety follow-up visit must occur before the first dose of the new therapy. If 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, 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. Any other evaluations and tests should be performed as clinically indicated.

Upon disease progression or initiation of other anti-cancer therapy, contact will be for survival only until the subject is off study (i.e., every 3 months [±4 weeks]); unless otherwise clinically indicated. See Study Calendar (Section **3.7**) for additional information. Any adverse events which are present at the time of discontinuation should be followed in accordance with the safety requirements.

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

3.6.1 Safety Follow-Up Visit

The safety follow-up visit should occur 30 days (±7 days) after the last dose of trial treatment, or before the initiation of a new anti-cancer treatment, whichever comes first. Required testing is as noted in the Study Calendars (Section **3.7**) All AEs that occur prior to the Safety Follow-Up Visit should be recorded. Patients with an ongoing, treatment-related AE of Grade > 1 will be followed until the resolution of the AE to Grade 0-1, stabilization of the AE in the opinion of the investigator, or until the beginning of a new anti-neoplastic therapy, whichever occurs first. SAEs that occur within 30 days of the end of treatment or before initiation of a new anti-cancer treatment should also be followed and recorded.

3.6.2 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. Every effort should be made to collect information regarding disease status until the start of new anti-neoplastic therapy, or disease progression. If the patient cannot return to the Clinical Center for any of these visits, a request will be made to have a local physician or laboratory collect a CBC with differential and send the results. If this is not possible, patients may be assessed by telephone or email for symptoms.

3.6.3 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 6 months (± 4 weeks) to collect information on new anti-cancer treatments received and to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first (see Study Calendar)

3.7 STUDY CALENDAR

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]	8 (-3)	15 (-3)	22 (-3)	1 (-3)	15 (-3)	Every 8 weeks [4]	Treatment discon/PD [5]	Day 30 (±7)	Every 60 or 90 days [6]	Every 6 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], LDH	X	X	X	X	X	X	X	X		X	X	X	
Serum Lipase and Amylase		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 (i.e., TSH, T4)	X	X	X				X			X	X	X	
Urinalysis	X	X	X				X			X			
Pregnancy Test (urine/serum; WOCBP)	X	X	X										
Hepatitis B and C, HIV Antibody, HTLV-1/2	X												
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-2Rα		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]	8 (-3)	15 (-3)	22 (-3)	1 (-3)	15 (-3)	Every 8 weeks [4]	Treatment discon/PD [5]	Day 30 (±7)	Every 60 or 90 days [6]	Every 6 months [7]
Pulmonary function tests (PFTs) [11]	X												
T, B, NK cell subsets		X		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	Refer to Section **5.1**										
Survival Status													X

NOTE: Any other tests should be performed as clinically indicated. See Section **3.2** for drug administration information. See Section **5.1** 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 mogamulizumab (via clinic or phone). If initiating new anti-cancer therapy within 30 days after last dose of mogamulizumab, 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] ± 2 days. Confirmatory scans should also be obtained 4 weeks following initial documentation of objective response.

[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.

[7] After disease progression or initiation of new anti-cancer therapy, contact for survival about 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).

[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. 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. FDG/ PETs to be done between C3 and C4 and at EOT.

[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 **5.1**. Prior biopsy specimen blocks will be used for CCR4 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.

3.8 COSTS AND COMPENSATION

3.8.1 Costs

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

3.8.2 Compensation

No direct compensation will be provided on the study.

3.8.3 Reimbursement

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

3.9 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

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

3.9.1 Criteria for removal from protocol therapy

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.
- 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 provide the study agent
- Study is cancelled for any reason
- Failure to maintain eligibility prior to starting treatment

3.9.2 Off-Study Criteria

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

- Study is cancelled for any reason

3.9.3 Lost to Follow-up

* A participant will be considered lost to follow-up if he or she fails to return for 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. 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 Sections **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 (not to include continuous intravenous fluids). If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the CRF.

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

Patients who are deemed to be at high risk for CNS involvement by the primary investigator and who have not received intrathecal prophylaxis prior to enrollment may receive it as clinically indicated after completion of the first cycle of therapy. Patients who have evidence of CNS involvement with lymphoma by flow cytometry and have no parenchymal lesions on brain imaging may receive intrathecal treatment as clinically indicated after completion of the first cycle of therapy.

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 mogamulizumab
- 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

5.1 SUMMARY

This study will attempt to use rhIL-15 to increase NK cell number and activity, thereby enhancing the ADCC of mogamulizumab in treatment of patients with relapsed and refractory MF/SS and ATLL. ADCC capacity of ex vivo PBMCs will be tested on CCR4-expressing cell lines before, during, and after protocol treatment. CCR4 mutation status will be determined for each patient by batch processing, and correlated with response and survival. Differences in circulating immune cell subsets associated with administration will be followed throughout treatment to both study the effects of combined rhIL-15/mogamulizumab therapy on the immune system, and to identify potential biomarkers that would be predictive of response. With the same goal in mind, immune cell subsets in the tumor microenvironment before and after treatment will be determined using single-cell RNA sequencing.

Sample	**Collection Details***	**Time Points**						**Supervising Laboratory/ Investigator**
		Baseline	C1 D8	C1 D15	C2-6 D1	C2-6 D15	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 mogamulizumab	• 3 x 10mL sodium heparin green-top tubes	(X)[2]	(X)[2]					Waldmann
Tissue immune cell subsets (comparison)	• 1 x 5mL sodium heparin green-top tube	(X)		(X)			(X)	Waldmann

Sample	Collection Details*	Time Points						Supervising Laboratory/ Investigator
		Baseline	C1 D8	C1 D15	C2-6 D1	C2-6 D15	Follow-up#	
Circulating tumor DNA, plasma banking	• 1 x 10mL K_2EDTA tube • 1 x 10mL Streck/BCT tube	X	(X)	X	(X)	(X)	X[3]	Waldmann (Leidos CSL)
PBMC banking	• 2 x 10mL sodium heparin green-top tubes	X	X	X	X	X	X	
Anti-IL-15 antibodies	• 1 x 4mL SST tube	X			X		X[1]	
CCR4 expression	• 2 x 10mL sodium heparin green-top tubes	(X)	(X)		(X)			Stetler-Stevenson (Laboratory of Pathology)
CCR4 mutation status	• 2 x 10mL sodium heparin green-top tubes	(X)						Raffeld (Laboratory of Pathology)
Tissue Samples								
CCR4 expression	• One core biopsy sample in formalin	X**		(X)				Pittaluga (Laboratory of Pathology)
CCR4 mutation status	• One core biopsy sample in formalin	X**		(X)				Raffeld (Laboratory of Pathology)
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)	Pittaluga (Laboratory of Pathology)
Single-cell RNA-Seq	• One core biopsy sample in RPMI 1640 with 10% human serum and antibiotics	(X)		(X)				Pittaluga (Laboratory of Pathology) and CCR single cell core
Other Samples								
Germline DNA	• Blood, Buccal Swab, or Saliva (preferred)	X						Waldmann (Leidos CSL)

Sample	Collection Details*	Time Points						Supervising Laboratory/ Investigator
		Baseline	C1 D8	C1 D15	C2-6 D1	C2-6 D15	Follow-up[#]	
(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 mogamulizumab, Baseline and C1D8 samples should be collected for at least one patient per dose level, and for at least three patients at the MTD [3] At each follow-up visit prior to disease progression, as specified in Section **3.6.2**.								

Note: If there is an optional biopsy for research in the protocol, then the patient will consent at the time of the procedure. If the patient refuses the optional biopsy at that time, the refusal will be documented in the medical record and in the research record.

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.

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

5.2.2 Blood Samples

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

5.2.2.1 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.

5.2.2.2 Antibody-dependent cell cytotoxicity (ADCC) of mogamulizumab

- 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 processing per established laboratory techniques, storage, and batch analysis by the Waldmann Laboratory.

5.2.2.3 Cell-free DNA (cfDNA), 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.

5.2.2.4 PBMC banking and tissue immune cell subsets (comparison)

- 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.

5.2.2.5 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.

5.2.2.6 CCR4 expression (peripheral blood flow cytometry, optional)

- Collect blood in two 10ml sodium heparin (green-top) 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: Flow Cytometry Laboratory, Laboratory of Pathology, NIH Clinical Center Bldg. 10/Room 3S240 for real-time processing; or delivered to: Leidos Biomedical Research, Inc. in Frederick, MD for storage.

5.2.2.7 CCR4 mutation status (peripheral blood, optional)

- Collect blood in two 10ml sodium heparin (green top) 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: Molecular Diagnostics Section, Laboratory of Pathology, NIH Clinical Center Bldg. 10/ Room 3S247 for real-time processing; or delivered to Leidos Biomedical Research, Inc. in Frederick, MD for storage.

5.2.3 Tissue Samples

5.2.3.1 CCR4 expression (tissue IHC) and mutation status

- 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 Laboratory of Pathology for analysis (IHC and mutation testing). If no prior biopsies are available at the time of screening, patients with MF/SS and ATLL 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).
- 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, normal saline, and/or 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, IHC testing for CCR4 expression by tumor cells and tumor-associated immune cells in addition to research testing (i.e., Waldmann Lab).

5.2.3.2 Tissue immune cell subsets and single-cell RNA-sequencing

- Collect 1-3 4mm punch biopsies (skin) or 1-3 18G core biopsies (lymph node/viscera) in RPMI 1640 with 10% human serum and antibiotics or normal saline.
- Lymphoid Malignancies Branch Clinical Research personnel will arrange for the samples to be delivered to NCI LP for processing to a single-cell suspension and storage. Samples will be batch processed by the single-cell sequencing core (NIH Clinical Center Bldg 10/Room 4B44).

5.2.4 Other Samples

5.2.4.1 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.

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 to be processed and DNA extracted/isolated per kit instructions and established techniques.

5.3 SAMPLE STORAGE, TRACKING, AND DISPOSITION

5.3.1 General

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

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

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

The PI will record any loss or unanticipated destruction of samples as a deviation. Reporting will be per the requirements of section **7.2**.

5.3.2 Lymphoid Malignancies Branch – Waldmann Laboratory

All samples that are noted in Section **5.1** to be analyzed by the Waldmann Laboratory will first be processed and stored at Clinical Support Laboratory, Leidos Biomedical Research, Inc. in Frederick, MD, as per Section **5.3.3**.

5.3.3 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 trials. The laboratory is CLIA certified for anti-IL15 and certain cytokine measurements and all laboratory areas operate under a Quality Assurance Plan with documented Standard Operating Procedures that are reviewed annually. Laboratory personnel are assessed for competency prior to being permitted to work with patient samples. Efforts to ensure protection of patient information include:

- The laboratory is located in a controlled access building and laboratory doors are kept locked at all times. Visitors to the laboratory are required to be accompanied by laboratory staff at all times.
- Hard copy records or electronic copies of documents containing patient information are kept in the locked laboratory or other controlled access locations.
- An electronic database is used to store information related to patient samples processed by the laboratory.
- The database resides on a dedicated program server that is kept in a central, locked computer facility.
- The facility is supported by two IT specialists who maintain up to date security features including virus and firewall protection.
- Program access is limited to specified computers as designated by the laboratory director. Each of these computers has a password restricted login screen.
- The database sample entry program itself is accessed through a password protected entry screen.
- Upon specimen receipt each sample is assigned a unique, sequential laboratory accession ID number. All products generated by the laboratory that will be stored either in the laboratory freezers or at a central repository facility are identified by this accession ID.
- Inventory information will be stored at the vial level and each vial will be labeled with both a sample ID and a vial sequence number.
- Vial labels do not contain any personal identifier information.
- Samples are stored inventoried in locked laboratory freezers and are routinely transferred to the NCI-Frederick repository facilities for long term storage.
- Access to stored clinical samples is restricted. Investigators establish sample collections under “Source Codes” and the 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.

5.3.4 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 Log book; 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.

5.4 SAMPLES FOR GENETIC/GENOMIC ANALYSIS

5.4.1 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.

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

Confidentiality for genetic samples will be maintained as described (Section **5.3**). In addition, a Certificate of Confidentiality has been obtained for this study.

5.4.3 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).

5.4.4 Genetic Counseling

Subjects will be contacted at this time 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. All data obtained during the conduct of the protocol will be kept in secure network drives or in approved alternative sites that comply with NIH security standards. Primary and final analyzed data will have identifiers so that research data can be attributed to an individual human subject participant.

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

Document AEs from the first study intervention, Study Day 1 through 30 days after the last intervention. 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 **7.2.1**.

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 Global Response Score (41) and modified severity weighted assessment tool (mSWAT) (19) for patients with MF/SS, and the International Consensus Meeting guidelines (42, 43) for patients with ATLL. Patient will be re-evaluated for response as outlined in the Study Calendar, Section **3.7**.

6.3.2 Response Criteria for MF/SS

Global Response (GR) score (**APPENDIX C**) will be used for assessing response in patients with CTCL (41). 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 (19) 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 (44), 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 11: 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.

6.3.3 Response Criteria for ATLL

Table 12: Response Criteria for Adult T-cell Leukemia-Lymphoma

Response	Definition	Lymph nodes	Extranodal masses	Spleen, liver	Skin	Peripheral blood	Bone marrow
CR*	Disappearance of all disease	Normal	Normal	Normal	Normal	Normal †	Normal
CRu*	Stable residual mass in bulky lesion	≥75% decrease ‡	≥75% decrease ‡	Normal	Normal	Normal †	Normal
PR*	Regression of disease	≥50% decrease ‡	≥50% decrease ‡	No increase	≥50% decrease	≥50% decrease	Irrelevant
SD*	Failure to attain CR/PR and no PD	No change in size	No change in size	No change in size	No change in size	No change	No change

RD/PD	New or increased lesions	New or ≥50% increase §	New or ≥50% increase §	New or ≥50% increase	≥50% increase	New or ≥50% increase‖	Reappearance
Not assessable							

CR: complete response, CRu: unconfirmed complete response, PR: partial response, SD: stable disease, RD/PD: relapsed disease/progressive disease

*Require each criterion to be present for a period of at least 4 weeks.

† Provided that <5% of flower cells remained, complete remission will be judged to have been attained if the absolute lymphocyte count, including flower cells is $< 4 \times 10^9$/L.

‡ Calculated by the sum of the products of the greatest diameters of measurable disease.

§ Defined by ≥ 50% increase from nadir in the sum of the products of measurable disease.

‖ Defined by ≥ 50% increase from nadir in the count of flower cells and an absolute lymphocyte count, including flower cells, of $> 4 \times 10^9$/L.

6.3.4 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).

6.3.5 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.

6.3.6 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.

6.3.7 Overall Survival

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

6.3.8 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.

6.3.9 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that

recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

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

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

6.4 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 once 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 (SAE)

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

- Death,
- A life-threatening adverse event (see **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 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 recorded 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/pages/viewpage.action?pageId=157942842

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

Reporting will be per the collaborative agreement.

8.5.1 CTEP

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

8.6 Reporting Pregnancy

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 6 months after the last dose of mogamulizumab.

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 90 days 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 mogamulizumab for up to 6 cycles
    - Frequency (number and percentage) of treatment-emergent AEs
- Secondary Endpoint(s):
    - Overall response rate (including CR and PR)

- ORR, TTP, and PFS by CCR4 mutation status (mutated versus wild type) and presenting diagnosis (MF/SS versus ATLL, MF versus SS, acute/chronic versus lymphoma subtype ATLL)
- Duration of response
- Progression-free, event-free, and overall survival
- Changes in percentage and absolute number of peripheral blood lymphocyte subsets
- Quantitation ADCC performed ex vivo on PBMCs obtained from the patients before and during treatment
- Characterization of changes in immune cell infiltrates of tumor deposits by immunohistochemical and molecular analysis of core biopsies obtained before and during treatment

10.2 SAMPLE SIZE DETERMINATION

The 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 6 to 9 patients will be enrolled at the MTD, so that a total of 12 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 both dose levels are evaluated with 6 patients per dose level and 12 total patients at the MTD, a maximum of 18 evaluable patients will be enrolled. Similarly, if all dose levels are evaluated with 3 patients per dose level and 12 total patients at the MTD, the minimum number of evaluable patients required will be 15. To account of unevaluable patients, accrual ceiling will be set at 20. It is expected that the accrual can be completed in 18 months.

A maximum of 18 patients will be enrolled over 18 months, at a rate of 1 patient 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 mogamulizumab.

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 for response. All patients who initiate treatment and receive at least one dose of study drug are considered evaluable for toxicity and will not be replaced.)

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 (45). 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, mogamulizumab, 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 (MF/SS or ATLL, and MF, SS, acute, chronic, or lymphoma subtype ATLL) and CCR4 mutation status (mutated versus wild-type).

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 MATERIAL TRANSFER AGREEMENT (MTA)- CTEP

An MTA with Division of Cancer Treatment and Diagnosis (DCTD) for the IL-15 was executed on September 11, 2019.

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 mogamulizumab 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 mogamulizumab 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 **12.4**), 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 as needed for the following: an independent assessment of whether an individual has the capacity to provide consent; assistance in identifying and assessing an appropriate surrogate when indicated; and/or an assessment of the capacity to appoint a surrogate. For those subjects that become incapacitated and do not have pre-determined substitute decision maker, the procedures described in NIH HRPP SOP 14E for appointing a surrogate decision maker for adult subjects who are (a) decisionally impaired, and (b) who do not have a legal guardian or durable power of attorney, will be followed.

12.4 Risk/ Benefit Assessment

12.4.1 Known Potential Risks

The potential risks of adding rhIL-15 to mogamulizumab include, in particular, infusion reactions (including chills, fever, hypotension, headache, flushing, dizziness), liver enzyme elevations, thrombocytopenia, and rash, particularly since the drugs are given concomitantly. As noted in Section **3.2**, premedication will be given during IL-15 infusions and before each mogamulizumab dose to reduce the risk of these AEs occurring. Patients will be monitored closely, and manufacturer recommendations for delaying and discontinuing mogamulizumab and initiating supportive therapy will be followed.

In addition to the tumor cells, CCR4 is also expressed on normal immune cells, immunosuppressive T regulatory cells (Tregs) in particular. While Treg depletion may have an anti-tumor effect, it also increases the risk of GVHD. In a post-marketing study conducted in Japan, among 29 patients who received mogamulizumab after a median of 59 days after allo-HSCT, seven who already had GVHD before receiving mogamulizumab did not experience worsening of their symptoms, and 5 of the 22 who did not have GVHD developed it after mogamulizumab.(46). International Consensus Group therefore recommends avoiding mogamulizumab within 50 days of allo-HSCT, but deemed it acceptable to use for patients with a more remote transplant history. (42).

12.4.2 Risks related Imaging

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.

12.4.3 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 assessments for research purposes. In summary, subjects may receive radiation exposure from up to seven (7) CT scans of the neck, chest, abdomen, and pelvis, and three (3) ^{18}F-FDG PET/CT scans.

The total radiation dose for research purposes will be approximately 12.7 rem.

12.4.4 Known Potential Benefits

The benefit of adding rhIL-15 to mogamulizumab in treatment of MF/SS and ATLL is unknown, but single-agent mogamulizumab has shown activity as outlined in Section **1.2.4**, is US FDA-approved for treatment of advanced MF/SS, and is recommended by the NCCN for treatment of relapsed/refractory ATLL.

12.4.5 Assessment of Potential Risks and Benefits

Mogamulizumab is FDA-approved for treatment of MF/SS and NCCN-recommended for treatment of ATLL. Since its primary mode of action is mediated by ADCC, agents that may enhance ADCC by increasing number and activity of Fc-binding effector cells — such as rhIL15 — could improve efficacy of mogamulizumab in these diseases. Although the clinical benefit of IL-15 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 mogamulizumab 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.

There have been no reports of severe capillary leak syndrome (CLS) when single-agent rhIL-15 was given via a continuous infusion. Of the first six patients treated with combination rhIL-15/mogamulizumab, one, with acute subtype ATLL, developed grade 4 CLS less than 24 hours after the first infusion of mogamulizumab and initiation of rhIL-15 infusion at DL2 (4 mcg/kg/day), which subsequently led to grade 4 acute kidney injury. Both had resolved after cessation of therapy and initiation of high dose steroids. This patient had baseline CLS which was disease-related, and which seems to have been worsened by the combination therapy. Although no definitive conclusions can be drawn from a single event, increased scrutiny will be given to similar patients with high circulating leukemic cell counts and baseline CLS, with close clinical follow-up for serious adverse events. Notably, there is no known effective treatment for such patients after combination chemotherapy and single-agent mogamulizumab.

12.5 CONSENT PROCESS AND DOCUMENTATION

The informed consent document will be provided to the participant or consent designee(s) (e.g., legally authorized representative [LAR] if participant is an adult unable to consent) 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) 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.

13 REGULATORY AND OPERATIONAL CONSIDERATIONS

13.1 STUDY DISCONTINUATION AND CLOSURE

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

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

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

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

13.2 QUALITY ASSURANCE AND QUALITY CONTROL

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

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

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

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

13.3 CONFLICT OF INTEREST POLICY

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

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) 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 stored at or below (-70°C).

14.1.6 Stability

14.1.6.1 Vials
Stability studies of the intact vials are ongoing.

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

14.1.7 Administration

For all dose levels, the dose of rhIL-15 will be diluted in the appropriate volume of 0.1% human serum albumin (HSA) in 5% dextrose in water, USP (D5W) 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 Appendix **3.2** 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	
Capillary leak syndrome	

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

14.1.9.2 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.

14.1.9.3 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.

14.1.9.4 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 MOGAMULIZUMAB (KW-0761, NSC# 791064)

14.2.1 Source/ Acquisition and Accountability

Mogamulizumab (Poteligeo®) is commercially available and will be purchased by the CCR and supplied to the patients enrolled on the study by the NIH Clinical Center Pharmacy Department.

14.2.2 Toxicity

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.

Version 2.3, September 15, 2019[1]

Adverse Events with Possible Relationship to KW-0761 (mogamulizumab) (CTCAE 5.0 Term) [n= 4759]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
CARDIAC DISORDERS		
		Chest pain - cardiac
		Myocardial infarction
		Myocarditis[2]
		Restrictive cardiomyopathy
GASTROINTESTINAL DISORDERS		
	Nausea	
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
	Fatigue	
	Fever	
	Flu like symptoms[2]	
IMMUNE SYSTEM DISORDERS		
	Allergic reaction	
		Anaphylaxis[3]
		Immune system disorders - Other (graft versus host disease)[4]
INFECTIONS AND INFESTATIONS		
	Infection[5]	
INJURY, POISONING AND PROCEDURAL COMPLICATIONS		
	Infusion related reaction[3]	
INVESTIGATIONS		
	Alanine aminotransferase increased[2,6]	
	Alkaline phosphatase increased[2,6]	
	Aspartate aminotransferase increased[2,6]	
	Blood bilirubin increased[2,6]	
	GGT increased[2,6]	
	Lymphocyte count decreased[2]	
	Neutrophil count decreased[2]	
	Platelet count decreased[2]	
	White blood cell decreased[2]	
METABOLISM AND NUTRITION DISORDERS		

Adverse Events with Possible Relationship to KW-0761 (mogamulizumab) (CTCAE 5.0 Term) [n= 4759]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
		Tumor lysis syndrome
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
	Arthritis[2]	
NERVOUS SYSTEM DISORDERS		
	Peripheral motor neuropathy[2]	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
	Pneumonitis[2]	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
		Erythema multiforme[2]
	Rash maculo-papular[2]	
		Skin and subcutaneous tissue disorders - Other (drug eruption, toxic skin eruption)[2]
	Skin hypopigmentation[2]	
		Stevens-Johnson syndrome[2]
		Toxic epidermal necrolysis[2]

[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 KW-0761 (mogamulizumab). Adverse events potentially related to KW-0761 (mogamulizumab) may be manifestations of immune-mediated adverse events. In clinical trials, most immune-mediated adverse reactions were reversible and managed with interruptions of KW-0761 (mogamulizumab), 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 KW-0761 (mogamulizumab), may manifest as fever, chills, shakes, itching, rash, hypertension or hypotension, or difficulty breathing during and immediately after administration of KW-0761 (mogamulizumab).

[4]Acute graft-versus-host disease has been observed in patients treated with KW-0761 (mogamulizumab) who subsequently received hematopoeitic stem cell transplants.

[5]Infection may include any of the infection sites under the INFECTIONS AND INFESTATIONS SOC.

[6]Symptoms of hepatic dysfunction may include Alanine aminotransferase increased, Alkaline phosphatase increased, Aspartate aminotransferase increased, Blood bilirubin increased, and GGT increased under the INVESTIGATIONS SOC.

Adverse events reported on KW-0761 (mogamulizumab) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that KW-0761 (mogamulizumab) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Anemia; Disseminated intravascular coagulation; Febrile neutropenia; Hemolysis; Thrombotic thrombocytopenic purpura

CARDIAC DISORDERS - Atrial fibrillation; Sinus tachycardia; Supraventricular tachycardia

EYE DISORDERS - Retinal vascular disorder

GASTROINTESTINAL DISORDERS - Abdominal pain; Cheilitis; Colitis[2]; Constipation; Diarrhea; Gastritis; Mucositis oral; Vomiting

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Death NOS; Edema limbs; Generalized edema; Malaise; Multi-organ failure

HEPATOBILIARY DISORDERS - Cholecystitis; Hepatic failure; Hepatobiliary disorders - Other (bile duct stone); Hepatobiliary disorders - Other (hepatitis)

INVESTIGATIONS - Blood lactate dehydrogenase increased[2]; CPK increased; Lipase increased; Serum amylase increased; Weight loss

METABOLISM AND NUTRITION DISORDERS - Acidosis; Anorexia; Dehydration; Hypercalcemia; Hyperglycemia; Hyperkalemia; Hypoalbuminemia; Hypocalcemia; Hypokalemia; Hypomagnesemia; Hyponatremia; Hypophosphatemia; Metabolism and nutrition disorders - Other (diabetes mellitus)

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthralgia; Flank pain; Generalized muscle weakness; Musculoskeletal and connective tissue disorder - Other (tendonitis); Myositis

NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Treatment related secondary malignancy

NERVOUS SYSTEM DISORDERS - Depressed level of consciousness; Encephalopathy; Headache; Nervous system disorders - Other (altered state of consciousness); Nervous system disorders - Other (cerebellar syndrome); Paresthesia; Seizure

RENAL AND URINARY DISORDERS - Acute kidney injury

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Adult respiratory distress syndrome; Cough; Dyspnea; Hypoxia; Pleural effusion; Respiratory failure

SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Dry skin; Erythroderma; Hyperhidrosis; Palmar-plantar erythrodysesthesia syndrome; Photosensitivity; Pruritus; Rash acneiform; Skin and subcutaneous tissue disorders - Other (lichenoid keratosis); Urticaria

VASCULAR DISORDERS - Hypertension[2]; Hypotension[2]

Note: KW-0761 (mogamulizumab) 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

Mogamulizumab is supplied as single-use 20 mg vials containing a sterile, clear, colorless solution (4 mg/mL). Mogamulizumab solution for infusion is formulated in 2.1 mmol/L sodium citrate buffer, 300 mmol/L glycine, and 0.2 mg/mL polysorbate 80 (Tween 80), pH 5.5, supplied in Type I glass vials.

Mogamulizumab solution for infusion must be diluted prior to administration. Do not shake the vials. To prepare the infusion solution add the dose volume of Mogamulizumab to an infusion bag containing 0.9% Sodium Chloride Injection, USP. PVC and non-PVC (polyolefin) IV bags may be used. The final concentration of the infusion solution must be between 0.1 mg/mL to 3.0 mg/mL.

14.2.4 Stability and Storage

Store intact vials between 2°C - 8°C (36°F - 46°F). Do not freeze. Protect from light by storing in the original box.

If a storage temperature excursion is identified, promptly return Mogamulizumab to between 2-8°C and quarantine the supplies.

After preparation, infuse the mogamulizumab solution immediately, or store under refrigeration at 2°C to 8°C (36°F to 46°F) for no more than 4 hours from the time of infusion preparation. Do not freeze. Do not shake.

14.2.5 Administration procedures

Infuse over at least 1 hour using an infusion set containing a low-protein binding 0.2 to 0.22 μm in-line filter. Do not co-administer other drugs through the same infusion line. Following the infusion, flush the IV line with normal saline.

14.2.6 Incompatibilities

No incompatibilities between mogamulizumab and polyvinylchloride (PVC) or non-PVC polyolefin bags and administration sets have been observed. No formal drug interaction studies have been performed with mogamulizumab. Please refer to the package insert and PDR for full drug interactions and toxicities.

Please refer to the mogamulizumab package insert for complete information.

15 REFERENCES

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16 APPENDICES

16.1 APPENDIX A: PERFORMANCE STATUS CRITERIA

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

16.2 APPENDIX B: ASSAY FOR ADCC

- Peripheral blood mononuclear cells (PBMCs) should be isolated by Ficoll-High-Paque Density Gradient Centrifugation.
- The viable cells should be viably frozen and stored in liquid nitrogen.
- The ADCC assay will be performed on the same occasion for all samples of a given patient.
- Vials of frozen cells will be thawed using standard procedures 18 hours before the assay in accordance with our experience with normal donors.
- 1.5 million of patient's PBMCs obtained before and on day 15 following IL-15 injection will be tested in aliquots as follows:
    - Tested alone
    - Tested with untreated PD-L1-expressing Raji cells and with PD-L1-expressing Raji cells coated with mogamulizumab 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 fo 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 aseptically in a laminar flow hood in compliance with all legal requirements and in accordance with guidelines of recognized organizations. Vials of IL-15 do not contain any preservatives.

0.1% human serum albumin (HSA) in 5% dextrose in water, USP (D5W), should be used for the dilutions listed below.

To prepare an IL-15 dose for Dose Level 1 (2 mcg/kg) *OR* Dose Level 2 (4 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**

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.

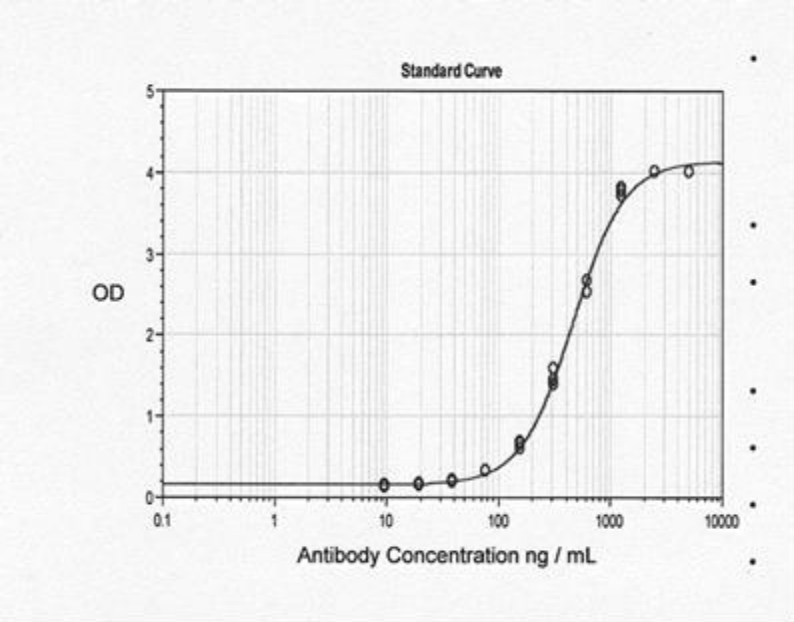
Patient's weight	IL-15 volume (490 mcg/ml)		Diluent volume		Total infusion volume (1 mcg/ml)	
	DL1	DL2	DL1	DL2	DL1	DL2
60 kg	0.27	0.51	129.73	249.49	130 ml	250 ml
75 kg	0.33	0.63	159.67	309.37	160 ml	310 ml
90 kg	0.39	0.76	189.61	369.24	190 ml	370 ml
105 kg	0.45	0.88	219.55	429.12	220 ml	430ml

Dose Level 1 (DL1) = 2 mcg/kg, Dose Level 2 (DL2) = 4 mcg/kg

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.