A

Cohort number	rhIL-15 Dose	Treatment	Weeks					
			1	2	3	4	5	6
Cohort 1	0.5mcg/kg/dose	rhIL-15	→	→				
		alemtuzumab			↓↓↓	→	→	→
Cohort 2	1 mcg/kg/dose	rhIL-15	→	→				
		alemtuzumab			↓↓↓	→	→	→
Cohort 3	2 mcg/kg/dose	rhIL-15	→	→				
		alemtuzumab			↓↓↓	→	→	→

B

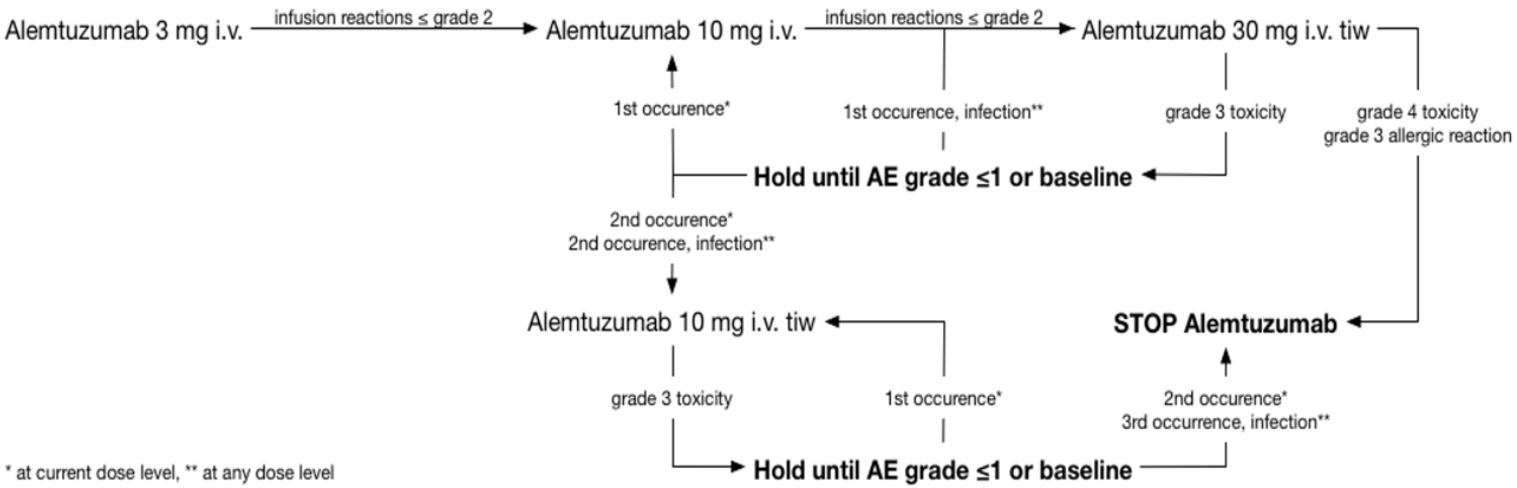

Figure 1. IL-15/alemtuzumab trial schema. **A.** Dose levels and treatment schedule. Red arrows: rhIL-15 given subcutaneously once daily Monday-Friday of each week. Downward arrows: alemtuzumab dose escalation, 3 mg i.v. Monday, 10 mg i.v. Tuesday, and 30 mg i.v. on Wednesday and Friday of Week 3. Blue arrows: alemtuzumab 30 mg i.v. on Monday, Wednesday, and Friday of Weeks 4-6. **B.** Alemtuzumab dose modification algorithm for non-hematologic toxicities at least possibly attributable to alemtuzumab. AE: adverse event.

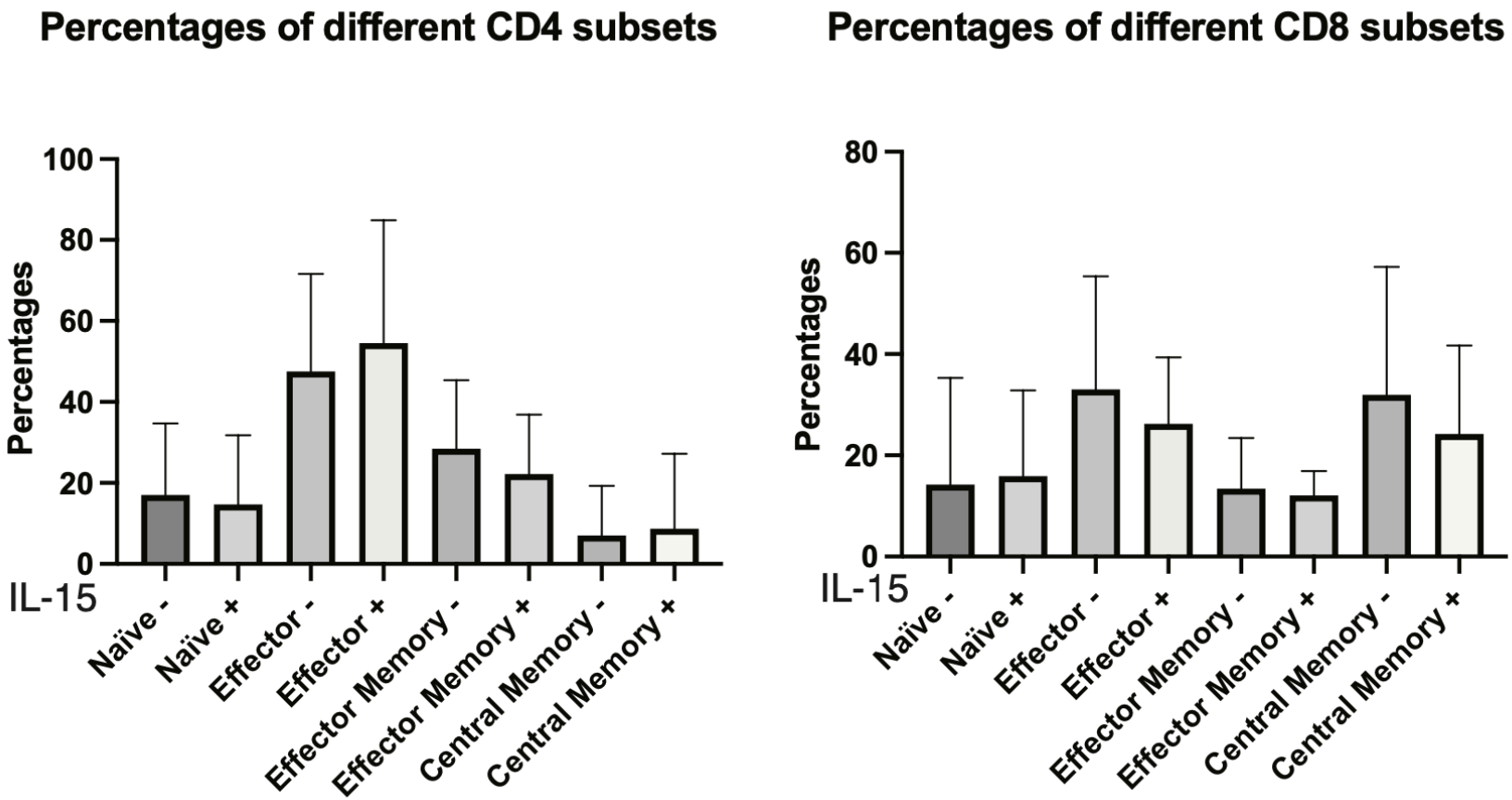

Figure 2: No difference in percentages of naïve, effector, effector memory and central memory among CD4+T and CD8+T cells was found between pre and post IL-15 treatement.

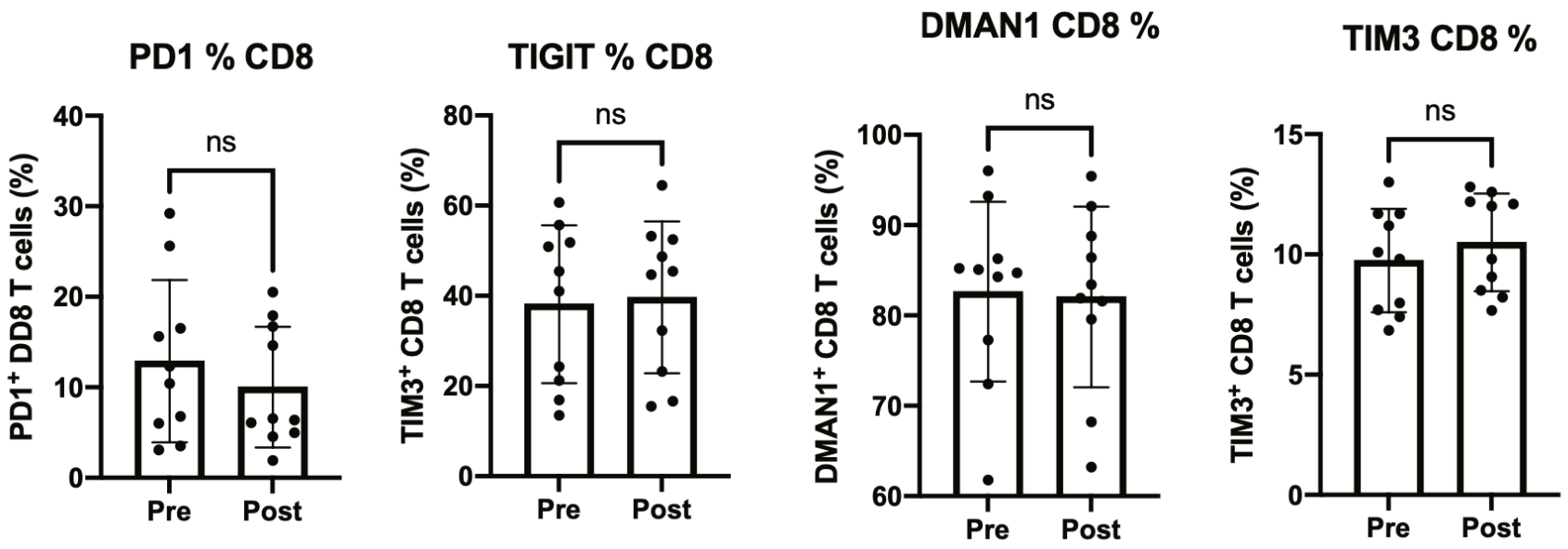

Figure 3: IL-15 treatments did not affect the phenotype of CD8+T cells

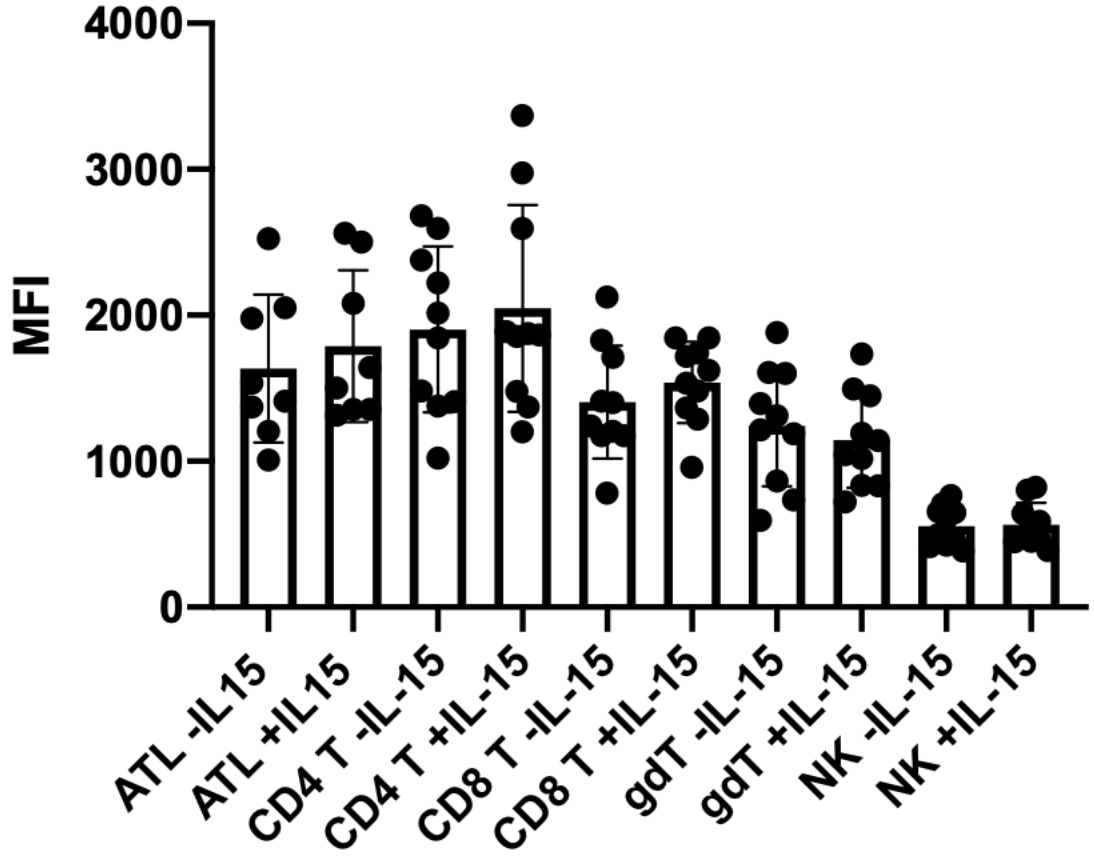

Figure 4: No change in CD52 expression on lymphocyte subsets was observed after IL-15 treatment

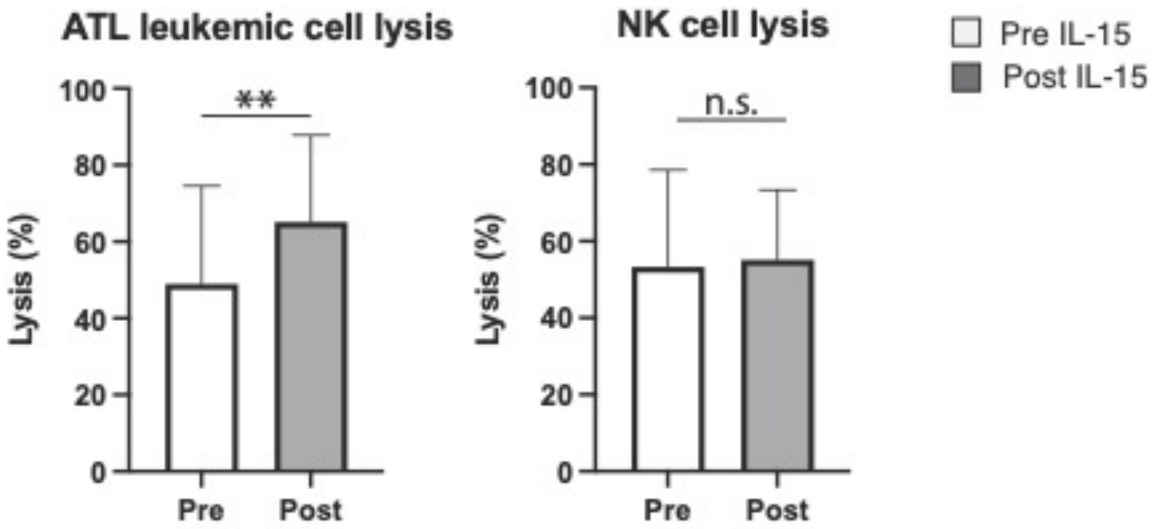

Figure 5: Lysis activity of *ex vivo* PBMCs against isolated *ex vivo* ATL cells and *ex vivo* NK cells before and after treatment with IL-15. PBMCs were incubated in presence or absence of anti-CD52 for 18hr. Disappearances of leukemic cells and NK cells were followed by cytometry. Calculation of lysis activities were based on ratio between target cells (ATL leukemic cells or NK cells) and CFSE labeled CD52- RAJI cells used as control.

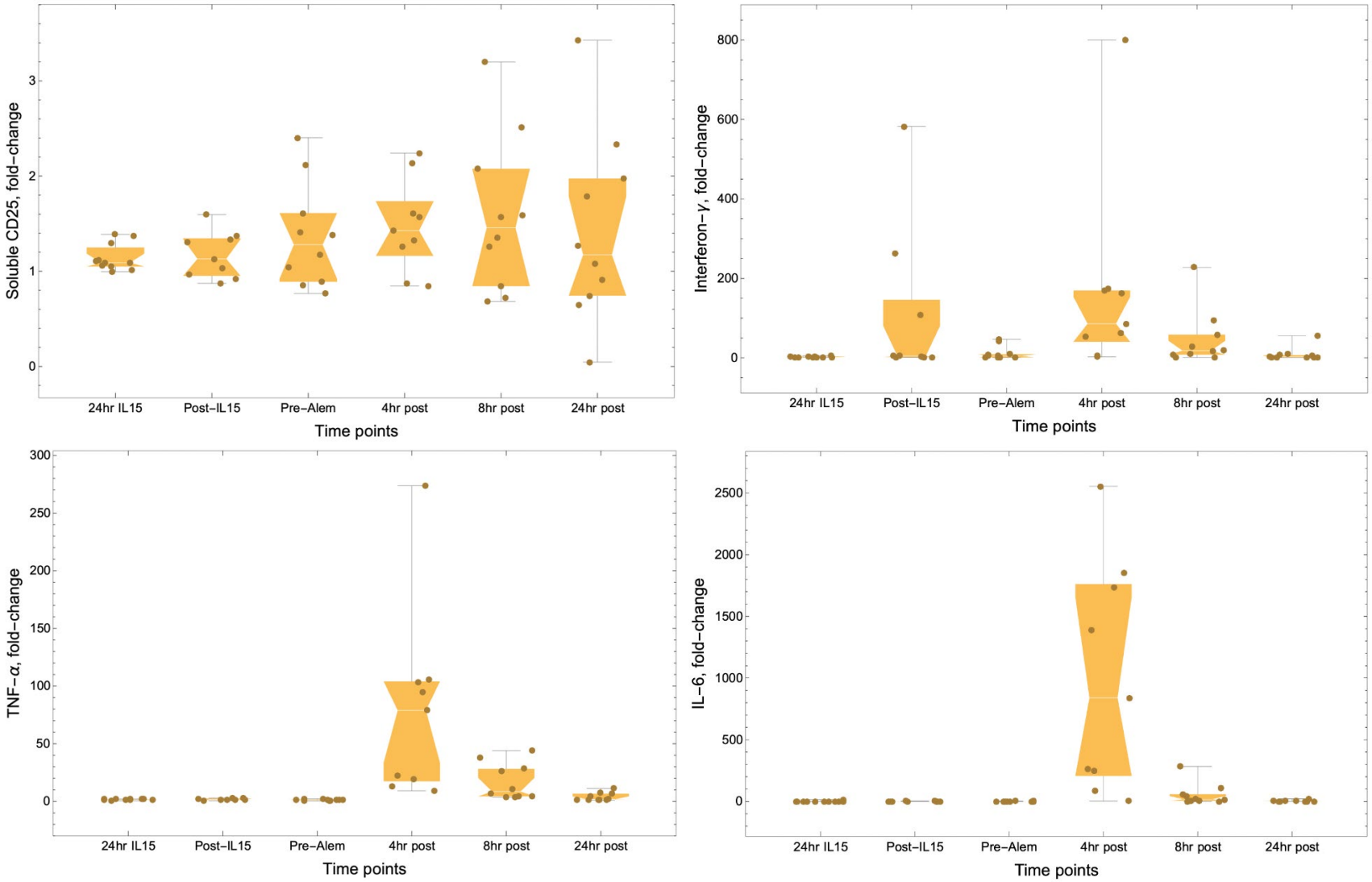

Figure 6: Changes in serum levels of soluble CD25, interferon- γ, tumor necrosis factor (TNF)-α and interleukin-6 after treatment with IL-15 and alemtuzumab.

Interleukin-15 augments NK cell-mediated antibody-dependent cell cytotoxicity of alemtuzumab in patients with CD52 positive T-cell malignancies

Supplementary Appendix 1

1 ELIGIBILITY ASSESSMENT AND ENROLLMENT

1.1 ELIGIBILITY CRITERIA

1.1.1 Inclusion Criteria

1.1.1.1 Age ≥ 18 years, no upper age limit.

1.1.1.2 Patients diagnosed with a leukemia or lymphoma as follows:

- Chronic or acute leukemia forms of HTLV-1 associated adult T-cell leukemia;
- Peripheral T-cell lymphoma (angioimmunoblastic, hepatosplenic, or not otherwise specified); or,
- Cutaneous T-cell lymphoma stage III or IV with circulating monoclonal cells (B1 or B2) and/or erythrodermia (T4)
- T-cell prolymphocytic leukemia (T-PLL)

NOTE: Diagnosis must be validated by the Pathology Department, NCI.

1.1.1.3 Patients must have measurable or evaluable disease.

NOTE: All patients with greater than 10% abnormal CD4+ homogeneous $CD3^{low}$ strongly CD25+ expressing cells, or greater than 5% Sézary/T-PLL cells, among the PBMCs in the peripheral blood will be deemed to have evaluable disease.

1.1.1.4 Abnormal T cells must be $CD52^+$ as assessed by flow cytometry or immunohistochemistry.

1.1.1.5 Patients must have a life expectancy of ≥ 2 months

1.1.1.6 Patients must have been refractory or relapsed following front-line therapy; those with CTCL or PTCL who have $CD30^+$ disease must have progressed during or after treatment with brentuximab vedotin or are unable to receive treatment due to allergy or intolerance.

1.1.1.7 Patients must have recovered to less than grade 1 or to baseline from toxicity of prior chemotherapy or biologic therapy and must not have had major surgery, chemotherapy, radiation or biologic therapy within 2 weeks prior to beginning treatment. **NOTE:** Exceptions to this include events not considered to place the subject at unacceptable risk of participation in the opinion of the PI (e.g., alopecia).

1.1.1.8 DLCO/VA and FEV – 1.0 > 50% of predicted on pulmonary function tests.

1.1.1.9 Adequate laboratory parameters, as follows:

- Serum creatinine of ≤ 1.5 x the upper limit of normal
- AST and ALT < 3 x the upper limit of normal
- Absolute neutrophil count ≥ 1,500/mm^3 and platelets ≥ 100,000/mm^3

1.1.1.10 ECOG ≤ 1

1.1.1.11 Patients must be able to understand and sign an Informed Consent Form.

1.1.1.12 All patients must use adequate contraception during participation in this trial and for 3 months following completing therapy.

1.1.2 Exclusion Criteria

1.1.2.1 Patients who have received any systemic corticosteroid therapy within 4 weeks prior to the start of therapy, or 12 weeks if given to treat graft versus host disease (GVHD), with the exception of physiological replacement doses of cortisone acetate or equivalent.

1.1.2.2 Patients who have undergone allogeneic stem cell transplantation and have required systemic treatment for GVHD (including but not limited to oral or parenteral corticosteroids, ibrutinib, and extracorporeal phototherapy) within the last 12 weeks

1.1.2.3 Clinical evidence of (parenchymal or meningeal) CNS involvement or metastasis. In subjects suspected of having CNS disease, a magnetic resonance imaging (MRI) scan of the brain and lumbar puncture should be done to confirm.

1.1.2.4 Documented HIV, active bacterial infections, active or chronic hepatitis B, hepatitis C.

- Positive hepatitis B serology indicative of previous immunization (i.e., HBsAb positive and HBcAb negative) or a fully resolved acute hepatitis B infection is not an exclusion criterion.
- If hepatitis C antibody test is positive, then the patient must be tested for the presence of HCV by RT-PCR and be HCV RNA negative.

NOTE: HIV-positive patients are excluded from the study. Alemtuzumab may produce a different pattern of toxicities in patients with HIV infection; in addition, the depletion of T cells produced by alemtuzumab may have adverse effects on HIV-positive individuals.

1.1.2.5 Concurrent anticancer therapy (including other investigational agents).

1.1.2.6 History of severe asthma or presently on chronic inhaled corticosteroid medications (patients with a history of mild asthma not requiring corticosteroid therapy are eligible).

1.1.2.7 Patients with smoldering and lymphomatous ATL.

1.1.2.8 Pregnant or nursing patients.

1.1.2.9 Patients who have previously received alemtuzumab are ineligible. **NOTE:** Patients with relapsed T-PLL who have achieved at least a partial response to prior alemtuzumab are eligible.

1.1.2.10 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, moderate/severe graft versus host disease, cognitive impairment, active substance abuse, or psychiatric illness/social situations that, in the view of the Investigator, would preclude safe treatment or the ability to give informed consent and limit compliance with study requirements.

2 SAFETY REPORTING

2.1.1 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)).

2.1.2 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 **2.1.3**)
- Inpatient hospitalization or prolongation of existing hospitalization
- 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.

2.1.3 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)

2.1.4 Severity

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

2.1.5 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.