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TITLE: Phase 1 Study of NT-I7 (rhIL-7-hyFc) for the Treatment of Kaposi Sarcoma in Patients With or Without Infection with HIV

Coordinating Center: Cancer Immunotherapy Trials Network (CITN),
Fred Hutchinson Cancer Center

Principal Investigator: Chia-Ching Wang, M.D.
Assistant Professor, Medicine
Division of Hematology-Oncology
University of California, San Francisco
995 Potrero Avenue
Building 80
San Francisco, CA 94110, USA
631-790-6155
Chia-Ching.Wang@ucsf.edu

Protocol Chair: Nancy E. Davidson, M.D.
Senior Vice President, Director and Professor
Clinical Research Division
Member, Fred Hutchinson Cancer Center
1100 Fairview Ave. N., D5-310
Seattle, WA 98109
206-667-6825
ndavidson@fredhutch.org

Participating Organization: CITN - Cancer Immunotherapy Trials Network

Interventional Radiologist: N/A

Statistician:

Axio Research
2601 4th Ave #200
Seattle, WA 98121
206-547-2829
206-547-4671

Study Coordinator: N/A

Responsible Research Nurse: N/A

Responsible Data Manager: N/A

NCI-Supplied Agent(s): N/A

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IND #: 156470

IND Sponsor: CITN

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<table>
<tr><th colspan="3">CONTACT INFORMATION</th></tr>
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Regulatory Submission Portal: (Sign in at https://www.ctsu.org, and select the Regulatory Submission sub-tab under the Regulatory tab.)

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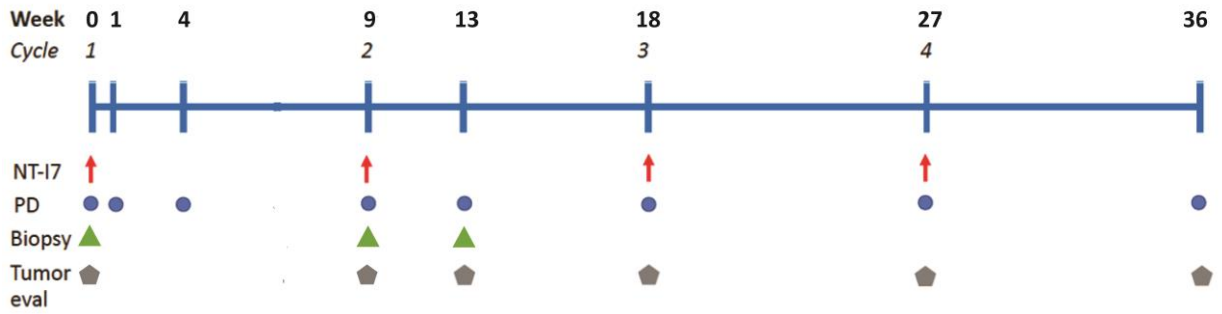
STUDY SUMMARY

Abbreviated Title	NT-I7 for treatment of Kaposi sarcoma (KS) in patients with or without HIV
Trial Phase	Phase 1
Clinical Indication	Kaposi sarcoma
Trial Type	Phase 1, open-label, non-randomized, single arm study with 3+3 dose escalation design
Type of control	N/A
Route of administration	Intramuscular (IM) Injections
Trial Blinding	None
Treatment Groups	The Safety Population will include all participants. The Efficacy Population will include the intent-to-treat population. Exploratory evaluation of response, stratified by HIV status and CD4+ T cell count greater than or less than 200 cells/µl, will be performed if there are at least 6 participants in a strata.
Number of trial participants	Up to 20 participants
Estimated duration of trial	30 months
Duration of Participation	Each patient will participate in the trial from the time the Informed Consent Form (ICF) is signed through the final protocol specific contact.

TRIAL SCHEMA

Treatment schema for the first 36 weeks of NT-I7 administration.



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1. OBJECTIVES

1.1 Primary Objectives

1.1.1 To determine the safety and adverse event profile of NT-I7 dosed at 480 µg/kg, 960 µg/kg, and 1200 µg/kg in patients with KS with or without infection with HIV, including estimation of the maximum tolerated dose (MTD) and/or the recommended Phase 2 dose (RP2D).

1.2 Secondary Objectives

1.2.1 To observe and record anti-tumor activity. The intent of treatment is to provide possible therapeutic benefit, thus patients will be monitored for tumor response and symptom relief in addition to safety and tolerability.

1.2.2 To evaluate the objective response rate (ORR) to NT-I7 in patients with KS with or without HIV.

1.2.3 To evaluate the duration of response (DOR), progression free survival (PFS), and overall survival (OS) in patients with KS with or without HIV.

1.2.4 To evaluate the effect of NT-I7 on the kinetics of absolute lymphocyte counts, CD4+ and CD8+ T-cells in blood and complete blood counts, and flow cytometry.

1.3 Exploratory Objectives

1.3.1 To evaluate the effect of NT-I7 on T-cell receptor (TCR) sequence diversity.

1.3.2 To evaluate immunogenicity of NT-I7 in patients with KS with or without HIV.

2. BACKGROUND

2.1 Study Disease(s)

2.1.1 Augmenting CD4 Immune Function for the Treatment of Kaposi Sarcoma

The hypothesis of the current trial is that IL-7 (NT-I7), known to substantially increase CD4+ T cell levels, will induce regressions of KS, similar to regressions observed with antiretroviral treatment (ART) associated increases in CD4+ T cell levels. CD4 lymphocytopenia and associated immune dysfunction are central to control of Kaposi sarcoma herpes virus (KSHV) and AIDS-associated Kaposi sarcoma (KS). T cell dysfunction is likewise implicated in the etiology of KS not associated with HIV. In the setting of HIV, the risk of KS is strongly associated with low CD4 counts. ART improves CD4 counts and leads to complete regression of disease in some but not all patients. Overall survival in AIDS-associated KS is associated with the level and possibly rate of CD4 T cell reconstitution. Delayed and incomplete CD4 immune

reconstitution are common problems in the management of HIV-associated KS and are often exacerbated by side effects of palliative chemotherapy. NT-I7 will rapidly correct the CD4+ T cell level. The essential question is whether increasing T cell levels will result in patient benefit.

2.1.2 Epidemiology of Kaposi Sarcoma

KS is an angioproliferative tumor associated with infection by Kaposi sarcoma-associated herpes virus (KSHV, also known as human herpesvirus 8 or HHV-8) (Gao et al. 1996). There are four established clinical variants of KS: (1) classic, (2) African (endemic), (3) AIDS-related, and (4) iatrogenic (typically transplant/immunosuppression-related). All four types have strong association with an incompetent immune system that is unable to control KSHV.

Classical KS was historically seen in older men (male-to-female ratio 3:1) of Mediterranean and Eastern European descent and is thought to be related to reduced control of KSHV in the setting of immunosenescence. There is evidence that it is related to inherited variations in immunomodulating genes (Kaasinen et al. 2013; Aavikko et al. 2015). It is frequently slow-growing (although aggressive and disseminated cases are seen), and survival rates are estimated at 70-80 percent.

Human immunodeficiency virus (HIV) infection-related KS accounts for greater than 80% of KS in the United States (Shiels et al. 2011; Engels et al. 2008). KS increases the risk of death by at least 2-fold in people with HIV. Although the incidence of AIDS-related KS in the US declined dramatically after the introduction of combination antiretroviral therapy (ART) in the early 1990s, the incidence of classic KS has remained relatively steady from 1975 – 2005. Survival rates from HIV–related KS are poorer than classic KS, despite improving substantially with the introduction of ART (Armstrong, Lam, and Chase 2013).

Iatrogenic KS is most commonly seen in solid-organ transplant recipients on immunosuppressive regimens, particularly those who receive cyclosporine A. It can present in both indolent and aggressive forms and is generally managed initially with withdrawal or modification of immunosuppression. Most cases of iatrogenic KS are seen in individuals with Mediterranean or African descent, again suggesting inherited variations in immunomodulation (Moosa 2005).

There are approximately 2,000 new cases of KS diagnosed in the US annually. Prevalence of KS in the US is estimated by SEER to be 29,000. Globocan estimates there are 4,000 cases a year in North America and Europe and estimates that the 5-year prevalence is 13,000. Five year overall survival is 54% for HIV-associated cases and 87% for HIV uninfected cases, so therefore 5-year prevalence underestimates the total prevalence of disease (Cancer). Many people with KS need intermittent therapy (most often chemotherapy) for life, which can be limited by cumulative toxicities.

In sub-Saharan Africa, KS is one of the most common tumors, in part because the seroprevalence of KSHV, the etiologic agent, ranges from 40-100% (compared to < 5% in the US). Globocan estimates the global incidence is 42,000 cases/year, and 5-year prevalence is 88,000 (Cancer). At the Uganda Cancer Institute, it is the third most common cancer. About 500 cases a year are treated at this one center alone. The incidence in HIV-positive patients on antiretroviral therapy

in sub-Saharan Africa is ~150:100,000 person-years, which is higher than that of prostate cancer in men in the US. In addition to HIV associated cases, there is a relatively high underlying prevalence of non-HIV associated cases, about 5/100:000 person-years in South Africa – likely there are even more in Uganda, which is similar to chronic lymphocytic leukemia (CLL) or diffuse large cell B cell lymphoma (DLBCL) incidence in the US.

2.1.3 T-cell Lymphocytopenia and Kaposi Sarcoma

KSHV was discovered in 1994 and is a necessary but insufficient cause of KS (Gao et al. 1996; Chang et al. 1994; Boshoff et al. 1995). The identification of a viral etiology of KS helped explain the long-observed association between KS and immunosuppression, specifically CD4+ T cell lymphopenia. Although KSHV infection likely happens early in life, the incidence of classic KS increases with advancing age, perhaps due to age-related immune senescence. Multiple studies have demonstrated significantly lower total lymphocytes and CD4+ T cells in patients with classic and HIV-related KS compared with age- and sex-matched controls (Touloumi et al. 1999). Progression in classical KS is linked to gradual decreases in lymphocyte count (Stratigos et al. 2005). HIV-associated KS is associated with increased frequencies of exhausted/immunosenescent T cells, and lower frequencies of naive T cells (Table 2) (Unemori et al. 2013).

Table 2. T-cell phenotype and KS risk: from Unemori P. et al. AIDS 2013.

	Kaposi's sarcoma-positive cases [median (range)] (n = 19)	Kaposi's sarcoma-negative controls [median (range)] (n = 47)	Age-adjusted P values (linear, quartile)
Percentage of $CD8^+$ T cells			
$CD57^+$	41.5 (30.2–49.3)	27.7 (19.4–38.3)	0.005, 0.005
$CD28^-$	60.5 (46.5–72.9)	51.3 (38.7–60.7)	0.044, 0.07
$CD27^+CD28^+CD45RA^+$	11.3 (6.8–14.8)	20.7 (14.1–30.1)	0.022, 0.025
$CD27^-CD28^-CD45RA^-$	35.0 (19.9–37.8)	19.5 (12.8–28.1)	0.05, 0.05
$CCR5^+$	43.1 (36.6–60.2)	28.3 (23.5–36.3)	<0.001, <0.001
Percentage of $CD4^+$ T cells			
$CD57^+$	7.4 (3.9–17.3)	3.7 (1.6–10.4)	0.07, 0.09
$CD28^-$	9.1 (5.0–20.9)	4.8 (2.0–11.9)	0.030, 0.05
$CD27^+CD28^+CD45RA^+$	23 (14.3–34.0)	32.2 (20.0–43.1)	0.11, 0.05
$CD27^-CD28^-CD45RA^-$	6.7 (3.9–20.4)	3.0 (1.2–9.0)	0.022, 0.04
$CCR5^+$	16.3 (9.4–28.9)	11.0 (7.7–16.1)	0.05, 0.008

Several lines of evidence support the notion that KS oncogenesis is associated with loss of T cell mediated control of KSHV, the viral cause of KS. Epidemiologic associations between KS incidence and immune suppression are strong, with the risk of KS increased several thousand-fold in the setting of HIV and organ transplantation (Grulich et al. 2007). Improvement and resolution of KS is associated with restoration of immune function, through the reversal of

iatrogenic immune suppression in patients with transplant-related KS or the initiation of ART and subsequent immune reconstitution in a subset of patients with HIV-associated KS (Penn 1995; Euvrard, Kanitakis, and Claudy 2003). Furthermore, restoration of T cell immunity with ART is accompanied by increases in T cell responses against KSHV, which in turn is associated with resolution of KS in some patients (Bihl et al. 2009).

HIV infection is the most common cause of acquired immunosuppression leading to KS. Untreated HIV infection leads to deterioration of CD4+ T cell counts over time. Within one year, 25% of people with untreated HIV will have a CD4+ T cell lymphocytopenia (CD4+ T cell < 350 cells/μL). Likewise, CD4+ immune reconstitution once starting ART occurs over months to years and is often incomplete. Circulating CD4+ T cell count recovery is often incomplete, even after a decade of therapy. The median time to CD4+ count recovery in people with a CD4+ count below 200 and between 200-350 cells/μL is 5 years and 2 years respectively. Approximately 40% of people with a CD4+ T cell nadir less than 200 cells/μL do not achieve a normal CD4+ T cell count (>500 cells/μL) even after a decade on ART (Kelley et al. 2009). In addition to decreased CD4+ T cell counts, people with HIV have additional T-cell dysfunction such as upregulated checkpoint proteins and perturbed T-cell repertoires (Day et al. 2006; Cockerham et al. 2014).

Although KS occurs across a broad range of CD4+ T cell counts in the ART era, the CD4+ T cell count remains strongly associated with the incidence of HIV-negative associated KS in men, despite being on ART (Lodi et al. 2010). This was validated in 2017 when CD4+ cell counts were shown to be a robust predictor of HIV-negative KS in North America (Dubrow et al. 2017). CD4+ count appeared even more significantly correlated with development of KS in other regions (IeDEA and EuroCoord 2017), although the "KS belt" was not included in the analysis. This risk was independent of ART, and suggested that despite starting ART, patients who did not recover their CD4+ T cell count remained at elevated risk. A 2005 study in King County, WA showed that HAART-era KS patients were as likely to have a low CD4+ T cell count as those in the pre-HAART era (Gallafent et al. 2005). [Note: HAART (Highly Active Antiretroviral Therapy) and ART (Antiretroviral Therapy) are interchangeable terms]. Another prognostic index for KS, developed in 2005, validated CD4+ count as one of 4 predictive criteria of developing KS in HIV (Stebbing et al. 2006).

2.1.4 Current Kaposi Sarcoma Therapy

In the US, KS continues to cause morbidity and mortality, and there is an urgent unmet clinical need for effective immunotherapeutic agents for KS. There are approximately 2,000 new cases of KS a year in the US, and a substantial number of these patients have incomplete response to therapy and/or relapsing remitting courses that require intermittent chemotherapy over a lifetime, especially patients with bulky disease. In a randomized study of liposomal doxorubicin versus paclitaxel as first line therapy, the median progression free survival (PFS) was approximately 16 months (Cianfrocca et al. 2010) and in the relapsed/refractory setting estimated PFS is approximately 6 months.

Furthermore, current therapy for KS is often characterized by limited response and toxicity (Bower et al. 2014). In patients with mild HIV-negative associated KS, disease frequently

responds to ART early in its course, but in advanced cases ART is insufficient. A stage-stratified approach recommends ART alone for limited cutaneous KS (Stage T0) and includes ART and chemotherapy for patients with more advanced KS (Stage T1) (Bower et al. 2014). In the US, patients with advanced KS are usually initially treated with liposomal anthracyclines (Gill et al. 1996; Stewart et al. 1998; Cooley et al. 2007; Cianfrocca et al. 2010; Northfelt et al. 1998). Patients who fail or do not tolerate this initial approach can be treated with paclitaxel (Welles et al. 1998; Tulpule et al. 2002).

Patients with KS often require treatment for many years. Prolonged chemotherapy administration is limited by cumulative toxicities, (i.e., bone marrow toxicities that may require growth factor support; cardiotoxicity from anthracyclines, drug-drug interactions between protease inhibitors and vinca alkaloids, immunosuppression from chemotherapy or radiation therapy, risk of secondary malignancies), which are more difficult to manage in low-resource settings. Patients with advanced KS often have poor outcomes with few long-term survivors (Mosam et al. 2012). While treatment of KS in the US and Europe is associated with clinical improvement rates of 50-80%, more than half of patients fail to achieve complete resolution of disease and up to 20% experience disease relapse within 1 year (Antman and Chang 2000; Dupin et al. 1999; Bihl et al. 2007; Nunez et al. 2001; Nguyen et al. 2008).

As development of KS is related to an incompetent immune system, there has been interest in moving away from cytotoxic, immunosuppressive therapies in favor of immunotherapy. There are several standard immunotherapy regimens used to treat patients with KS. Interferon-alpha 2b (Intron A®) is FDA approved for AIDS-associated KS. Response rates at a dose of 30 million units intramuscularly three times a week range from 29% to 71% and increase with increasing CD4+ T cell counts and higher CD4+/CD8+ T cell ratios. Use of Intron-A is limited due to common adverse events such as “flu-like symptoms” including fevers, headache, myalgia and fatigue, as well as severe depression in some cases. Interferon-alpha is most effective in patients with a CD4+ T cell count >150 cells/µL(Krown et al. 2002). More recently, pomalidomide has been shown to have a 73% response rate in a heavily pre-treated patient population in a Phase I/II study (Polizzotto 2015; Polizzotto et al. 2014). Its activity in part appears to be through increases in the number of CD4+ and CD8+ T cells and the proportion of activated and central memory cells and decreased senescence. These promising data suggest that immunotherapy may be an effective approach to KS, and one that should be attempted prior to immunosuppressive or cytotoxic therapy.

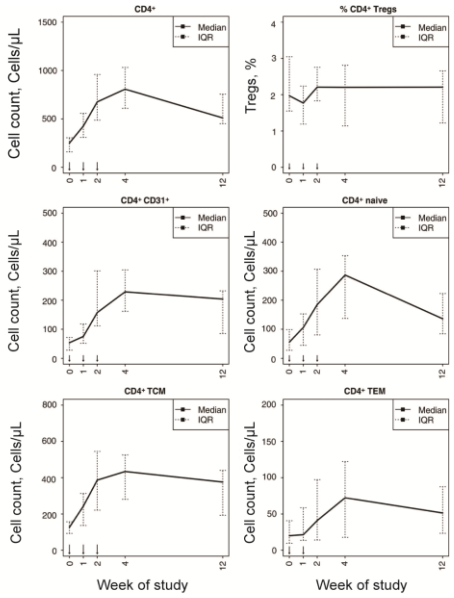
2.1.5 Interleukin-7 and HIV

The cytokine interleukin-7 (IL-7) plays an important role in T cell development and proliferation (Schuler, Hammerling, and Arnold 2004), and regulates T cell homeostasis throughout life. IL-7 stimulates increases in T cell proliferation, including naïve T cells (Mackall, Fry, and Gress 2011), and prolongs survival of mature T cells, resulting in elevated CD4+ and CD8+ T cell numbers. Both B and T cell development depends on a functional IL-7 receptor (Puel and Leonard 2000). Recombinant interleukin-7 (IL-7) has been shown in mice to reverse thymic atrophy and increased thymic output (Mackall, Fry, and Gress 2011). A phase I study of recombinant human IL-7 (rhIL-7) in 16 cancer patients suggested that rhIL-7 increased the

numbers of naïve and central memory cells, independent of age (Sportes et al. 2008). Another study showed evidence that IL-7 may increase expression of B cell costimulatory molecules on T helper cells, leading to abnormal B cell differentiation (Chiodi et al. 2017).

Figure 1. CD4 kinetics after administration of subcutaneous injections of r-hIL-7 20 µg/kg administered weekly for 3 weeks

Detailed immune response in INSPIRE 2 patients for total CD4+ T cells, CD4+ regulatory T cells (Tregs), CD4+CD31+ T cells, and CD4+ naive, central memory (TCM), and effector memory (TEM) T cells, from baseline (week 0) to week 12. Abbreviation: IQR, interquartile range.



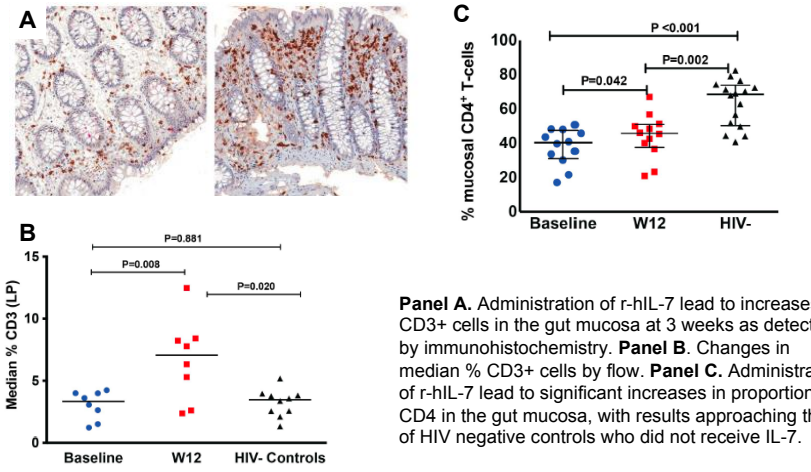
Clinical Infectious Diseases, Volume 62, Issue 9, 1 May 2016, Pages 1178–1185, https://doi.org/10.1093/cid/ciw065

In HIV infection, increased levels of IL-7 drive T cell-cycle entry and expansion (Levy et al. 2009; Sereti et al. 2009), resulting in increased numbers of circulating T cells of central memory and naïve phenotypes. This effect is sustained, with peaks generally seen at 14 days (Levy et al. 2012; Thiebaut et al. 2016). Under lymphopenia, there is evidence that T cells upregulate the STAT1 signaling pathway, increasing proliferation in an IL-7 dependent manner. During HIV infection, there is speculation that virus may exploit this pathway, leading to the homeostatic dysregulation of the T cell pools observed in these patients (Le Saout et al. 2017). Patients with lower CD4+ T cell counts have been shown to have higher amounts of IL-7 mediated homeostatic proliferation and higher rates of HIV-negative infected T transitional memory cells (Chomont et al. 2009). Nonetheless, in chronic uncontrolled HIV, physiologic doses of IL-7 are unable to prevent CD4+ lymphocytopenia. Furthermore, lymphopenia-inducing insults that may occur in the treatment of KS such as anti-neoplastic or radiation treatment could result in a prolonged CD4+ T cell depletion (Hakim et al. 2005). In this setting, lymphopenia is not efficiently supported by a physiological increase in IL-7 levels (Guimond et al. 2009). IL-7 administration is very potent at producing "new T cells" such as naïve T cells and recent thymic emigrants. In preclinical studies, IL-7 therapy showed significant effects on T cell immune reconstitution in mice (Mackall and Gress 1997) and primates (Beq et al. 2006; Fry et al. 2003; Storek et al. 2003). Recent clinical trials in humans have demonstrated the potential of IL-7 to expand and protect CD4+ and CD8+ T cells (Mackall, Fry, and Gress 2011).

Short acting recombinant human IL-7 (glycosylated rhIL-7, CYT107 or non-glycosylated rhIL-7, CYT99007) has been evaluated at the dose range of 3~60µg/kg with subcutaneous or intramuscular injection three times per week or weekly for 3 weeks in over 300 patients including patients with chronic HIV or HCV infections, patients with refractory solid tumors, and patients after allogeneic stem cell transplantation (Rosenberg et al. 2006; Sportes et al. 2008; Levy et al. 2009; Sereti et al. 2009; Sportes et al. 2010; Levy et al. 2012; Perales et al. 2012; Vandergeeten et al. 2013; Alstadhaug et al. 2014; Gasnault et al. 2014; Thiebaut et al. 2014;

Sospedra et al. 2014; Thiebaut et al. 2016; Tredan et al. 2015; Merchant et al. 2016; Miskin et al. 2016; Sheikh et al. 2016). In most studies, a marked increase in peripheral T cells and broadening of TCR diversity were seen to be dose-dependent, and rhIL-7 was well tolerated. The most common adverse events (AEs) related to rhIL-7 were mild to moderate (no AEs were above grade 2) and were primarily fever and cutaneous reactions at the injection site. In the studies of rhIL-7 in HIV, administration led to CD4 expansion in the blood (Figure 1) and gut associated lymphoid tissue (Figure 2).

Figure 2. Effects of subcutaneous injections of r-hIL-7 on gut mucosal T-cells at week 12 in people with HIV



Panel A. Administration of r-hIL-7 lead to increases in CD3+ cells in the gut mucosa at 3 weeks as detected by immunohistochemistry. **Panel B**. Changes in median % CD3+ cells by flow. **Panel C.** Administration of r-hIL-7 lead to significant increases in proportion CD4 in the gut mucosa, with results approaching that of HIV negative controls who did not receive IL-7.

PLoS Pathogens, Volume 10, Issue 1, Jan 2014.
https://journals.plos.org/plospathogens/article?id=10.1371/journal.ppat.1003890

These results support the previously reported safety profile of rhIL-7 in both HIV infected patients and patients with advanced cancer (Sportes et al. 2010). The favorable safety profile of IL-7, in contrast to the severe toxicities of IL-2 (e.g. hematological toxicities, capillary leak syndrome) (Higuchi et al. 1991), indicates that rhIL-7 is a promising therapeutic option that deserves further clinical investigation. It is noteworthy that during chemotherapy, there were no reports of any patients treated with rhIL-7 experiencing any severe hematological AEs (Tredan et al. 2015). The ability of rhIL-7 (CYT107, RevImmune Inc.) to increase T cell levels with minimal toxicity have been validated in CITN studies testing CYT107 following Provenge in patients with prostate cancer (ClinicalTrials.gov Identifier: NCT01881867; Manuscript in preparation 2019). HIV persists in T central memory cells in patients on ART, a reservoir which is maintained through low-level antigen-driven proliferation and is slowly depleted with time. IL-7 may have a theoretical potential to affect proliferation of HIV infected reservoir cells themselves. However, detrimental effects on the management of HIV have not been observed in patients with HIV treated with recombinant IL-7. An *ex-vivo* study showed that, despite inducing the proliferation of HIV-negative infected circulating CD4+ T cells, exogenous IL-7 administration had minimal effect on viral production in the CD4+ T cells from virally suppressed patients (Vandergeeten et al. 2013). Additionally, it did not disrupt viral latency in resting, latently infected CD4+ T cells from virally suppressed patients.

About half of the patients had a small but measurable increase in viral production (>10 HIV RNA copies/mL) following IL-7 stimulation, but this represented only 10% of the production induced by T cell receptor (TCR) stimulation (Vandergeeten et al. 2013).

A phase I study evaluating IL-7 in patients with HIV demonstrated CD4+ and CD8+ T cell expansion for at least 48 weeks. Half of these patients also experienced increases in low level

HIV viremia ("blips") that were of unclear significance. This was followed by a phase II study of IL-7 in patients with HIV observed HIV RNA blips >50 copies/mL, occasionally exceeding 200 copies/mL, which prompted delay of subsequent IL-7 doses (Thiebaut et al. 2016). The clinical relevance of these viral "blips" is unclear; it is possible that it represents expansion of T cells but not replication-competent HIV. Experience to date suggests "blips" are short lived, lasting less than 4 weeks in ACTG5214.

2.2 CTEP IND Agent: N/A

2.3 Other Agent(s)

2.3.1 IL-7-hyFc (NT-I7; HyLeukin-7, NeoImmuneTech, Inc.), [also being developed as GX-I7 by Genexine, Inc.]

NT-I7 (the International Nonproprietary Name is efineptakin alfa) is a long-acting human IL-7 cytokine. It consists of human IL-7 and a hybrid crystallizable fragment (hyFc) region, which extends the half-life of NT-I7. HyFc is composed of the human IgD hinge region fused to the N-terminal region of homologous constant region domain 2 (CH2) from IgD, which is in turn is fused to the C-terminal region of CH2 and the entire homologous constant region 3 (CH3) of human immunoglobulin IgG4. A detailed structural diagram of NT-I7 is shown in the NT-I7 Investigator's Brochure.

2.3.2 Studies

Data from completed and ongoing clinical studies showed that NT-I7 has demonstrated a well-tolerated safety profile, and administration of NT-I7 led to a dose-dependent increase in the peripheral CD4+ and CD8+ T cells (naïve [TN], T_{EM}, central memory cells [T_{CM}], and terminally differentiated effector memory [T_{EMRA}]) and natural killer T (NKT) cells, but there was no dose-dependent increase in B cells. Exposure and pharmacodynamic effect were greater following intramuscular (IM) than subcutaneous (SC) administration.

2.3.2.1 Completed Study of GX-I7-HV-001

A first in human (FIH) Genexine trial (Study No. GX-I7-HV-001) in healthy volunteers was conducted with a single dose of NT-I7 with a dose range of 20 µg/kg (cohort 1, SQ) to 60 µg/kg (cohort 2, SQ; and 60 µg/kg cohort 3, IM). NT-I7 treatment was well tolerated in healthy volunteers after single SC or IM administration. GX-I7-HV-001 was a randomized, double-blind, placebo-controlled, dose-escalation, Phase 1 study to assess safety, tolerability, pharmacokinetics (PK), and pharmacodynamics after a single SC or IM administration of NT-I7 in healthy volunteers. Eligible subjects randomly received NT-I7 or placebo in an 8:2 ratio at one of the following doses: 20 µg/kg SC, 60 µg/kg SC, or 60 µg/kg IM.
NT-I7 was slowly absorbed, particularly after SC administration (time to maximum concentration [T_{max}]: 36 to 42 hours postdose) and was slowly removed from the body ($T_{1/2}$: 48 to 112 hours), resulting in a flat PK profile, typically seen in biologics. IM NT-I7 was more rapidly absorbed than SC NT-I7 (median T_{max}: 4 hours vs 36 hours postdose for IM vs SC, respectively), and exposure was ~2 times larger following IM than SC administration at the same

dose of 60 μg/kg, although the difference was not statistically significant. The PK parameters of NT-I7 were more variable after IM administration than SC injection. After SC administration, the exposure to IL-7 was increased in a dose-proportional manner. PK parameters are summarized in NT-I7 Investigator's Brochure.

The pharmacodynamics assessments as observed by the ALC was increased in a dose-dependent manner after NT-I7 IM or SC administration (111.4% IM vs 75.1% SC for percent change from baseline at the same dose of 60 μg/kg). The increase in ALC peaked approximately 3 weeks after administration of NT-I7, and it lasted over several weeks. An initial 40% to 60% decrease in ALC was seen in all subjects within 4 days after NT-I7 administration was likely due to "homing effect". Pharmacodynamic parameters are summarized in NT-I7 Investigator's Brochure.

Further, T-cell counts were also increased following treatment with NT-I7. Cell proliferation was observed for all CD4+ and CD8+ naïve T cells, effector memory T cells (T_{EM}), central memory T cells (T_{CM}), and terminally differentiated effector memory T cells (T_{EMRA}) at 168 hour post-dose (Day 7), and the most robust response was observed in NT-I7 60 μg/kg IM group.

The Cohort 3 60 μg/kg IM results demonstrated that there was a substantial increase in the number of CD4+ and CD8+ T cells, naïve T cells, central memory (CM), effector memory (EM), terminally differentiated effector memory (T_{EMRA}) T cells and NKT cells, but no increase in the number of B cells, NK cells, monocytes or regulatory T cells. Ki-67+ cells were also analyzed to see whether there was proliferation of cells in response to NT-I7 administration. The results showed that Ki-67+ naïve, EM, CM and TEMRA CD4/CD8 T cells reached maximum counts in approximately 7 days post-administration and reduced to baseline approximately 21~28 days after administration. Effects on absolute lymphocyte counts and CD4+ and CD8+ T cell subsets in a phase I study are noted in Figure 3. Additionally, IL-7 receptor expression after IL-7 administration by both the CD4+ and CD8+ T cells were reduced to minimal levels within 3 days after NT-I7 administration and returned to baseline in approximately 7~10 days after administration. To make CD4+ and CD8+ T cells traffic to distant sites such as lymph nodes or tumor sites, chemokine receptors need to be over-expressed. Three types of chemokine receptors were analyzed, and it was found that CCR5 expression by both CD4+ and CD8+ T cells was increased in a dose-dependent manner. This effect was highest in Cohort 3.

Most subjects (n=22, 91.7%) who received NT-I7 developed anti-drug antibody (ADA) during the study period, while there was no ADA detected in the placebo group. Appearance of ADA/NAbs under a single dose of NT-I7 did not impact the PK profile in the study with healthy volunteers. Neutralizing ADAs (NAbs) were observed in 41.6% (10/24) of the subjects 1 month after NT-I7 administration, and 45.8% (11/24) 2 months after NT-I7 administration, and 1 subject harbored neutralizing ADAs 5 months after NT-I7 administration. However, the presence of ADA and NAbs did not appear to affect drug exposure, safety profile, or pharmacodynamic parameters of NT-I7. Peripheral ALC was monitored in these participants, when possible, up to 17 months. There was no detected lymphopenia or any other evidence of detrimental immunologic effects in these participants. For more information, refer to NT-I7 Investigator's Brochure.

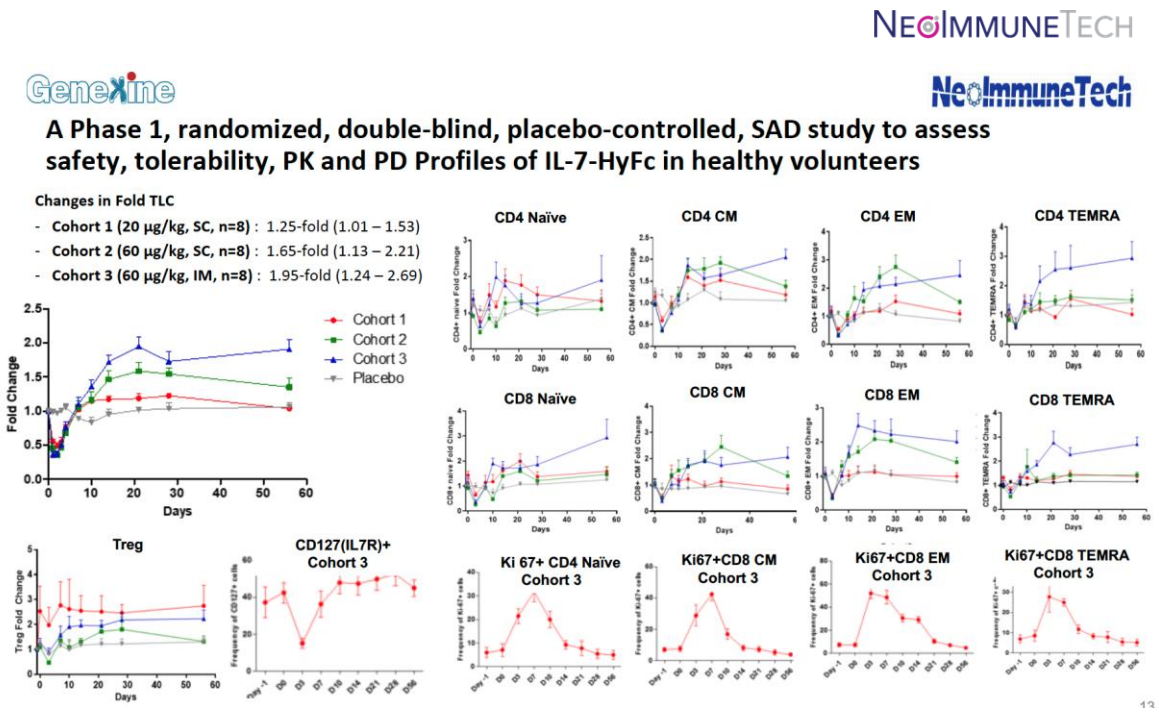


Figure 3. Effects of NT—I7 on absolute lymphocyte counts, proliferation rates, and CD4+ and CD8+ T-cell subsets.

2.3.2.2 Completed Study GX-I7-CA-003

GA- I7-CA-003 was a Phase 1b, single-agent, open-label, 3+3 dose-escalation study to determine the Recommended Phase 2 Dose (RP2D) and to evaluate safety, tolerability, PK, and pharmacodynamics of NT-I7 in subjects with locally advanced or metastatic solid tumors. GX-I7 (an alternative name for NT-I7) was administered IM on Day 1 of each 21-day cycle at doses of 60 µg/kg, 120 µg/kg, 240 µg/kg, 480 µg/kg, 720 µg/kg, 960 µg/kg, 1200 µg/kg, and 1700 µg/kg.

Pharmacodynamic data from the study showed ALC and naïve/less differentiated memory subsets of CD4+ and CD8+ T cells increased in a dose-dependent manner after NT-I7 administration. T cell increases were most prominent in the 1200 µg/kg and 1700 µg/kg dose groups. The levels of endogenous IL-7 remained at normal levels without any significant change.

The dose-dependent increase in exposure with GX-I7 was observed in all dose groups. Following IM administration, the GX-I7 T_{max} was 11 to 47.5 hours depending on dose, with an elimination half-life of 60.8 to 139.7 hours. C_{max} and AUC_{last} increased with increasing dose of study drug, and both increased in a dose-proportional manner.

In GX-I7-CA-003, immunogenicity was assessed by measuring ADAs and nAb on all subjects. No subject was positive 8 days after the first administration of NT-I7, and ADAs and nAb were detected in all subjects by the third administration of NT-I7 (regardless of dose or dosing

interval). All subjects remained positive for both while continuing to receive NT-I7. Endogenous IL-7 levels were maintained at normal levels without significant change, and there were no specific AEs related at normal levels without significant change, and there were no specific AEs related to ADA. The presence of ADAs did not appear to affect drug exposure, pharmacodynamic endpoints, or safety of the drug with repeated dosing in patients with solid cancers.

2.3.2.3 Other Studies

ABTC-1403 (also known as NIT-104) is an ongoing Phase 1 dose-escalation and pilot study of the effect of NT-I7 on CD4 cell counts in subjects with high grade gliomas and severe treatment-related CD4 lymphopenia after concurrent radiation therapy (RT) and treatment with temozolomide (TMZ). The study is ongoing in the U.S.

NIT-106 is a Phase 1b/2a, open-label study to evaluate anti-tumor efficacy and safety and tolerability of NT-I7 in combination with anti-PD-L1 (atezolizumab) in subjects with anti-PD-1/PD-L1 naïve or relapsed/refractory high-risk skin cancers.

NIT-109 is Phase 2 study of NT-I7 in combination with nivolumab in subjects with relapsed/refractory gastric or gastro-esophageal junction or esophageal adenocarcinoma who progressed on or were intolerant to 2 or more prior lines of systemic therapy.

NIT-110 is a multicenter, open-label, Phase 1b/2a study of NT-I7 in combination with pembrolizumab in subjects with relapsed/refractory advanced solid tumors.

NIT-112 is a multicenter, Phase 1b study evaluating safety, tolerability, and preliminary anti-tumor activity of NT-I7 administration following standard of care tisagenlecleucel CAR T cell therapy in subject with relapsed/refractory large B cell lymphoma.

NIT-116 is a multicenter, double-blind, randomized, placebo-controlled Phase 1, single dose, dose escalation study of NT-I7 in adults with mild COVID-19.

NIT-119 is a multicenter, open-label, single-arm Phase 2 study evaluating anti-tumor efficacy and safety of NT-I7 in combination with atezolizumab in subjects with previously untreated, PD-L1-expressing, locally advanced or metastatic non-small cell lung cancer.

More details are provided in the NT-I7 Investigator's Brochure.

2.3.3 Benefits and Risks Conclusions

Safety, pharmacodynamic, and PK data for NT-I7 are available from two completed and seven ongoing studies. Based on the available data, it can be concluded that:

1) NT-I7 was well tolerated in healthy volunteers and adult subjects with advanced solid tumors;
2) NT-I7 was well tolerated in combination with checkpoint inhibitors (CPIs) in adult

patients with relapsed/refractory solid tumors;
3) NT-I7 was slowly absorbed and eliminated, resulting in a flat PK profile, regardless of route of administration;
4) IM administration of NT-I7 resulted in more rapid absorption and had higher exposure to NT-I7 than did SC administration;
5) NT-I7 led to a dose-dependent increase in CD4+ and CD8+ T cells (naïve T cells, T_{SCM}, T_{EM}, T_{CM}, T_{EMRA}) and NK cells, but there was no dose-dependent increase in B cells;
6) IM administration of NT-I7 resulted in a more pronounced increase in lymphocytes over SC administration.

The well-tolerated safety profile seen with NT-I7 in humans and the ability of NT-I7 to increase naïve T cells, T_{EM}, T_{CM}, T_{EMRA} in cancer patients as well as the promising preclinical data of NT-I7 in combination with CPIs support further clinical investigation of NT-I7 in cancer patients to enhance anti-tumor activity.

More detailed information about the known and expected benefits and risks and reasonably expected AEs may be found in the NT-I7 IB.

2.4 Rationale

2.4.1 Risk Benefit Analysis in HIV associated Kaposi Sarcoma

Cancer is the leading cause of death in people with HIV. KS is associated with 40% mortality in HIV clinics in the US and Canada. Scalable T cell modulating therapies with minimal toxicities are highly desirable for KS. Based on the literature to date, the benefits of an effective immunotherapy for KS outweigh the theoretical risk of increasing the HIV reservoir. We hypothesize that NT-I7 will have a favorable therapeutic index in people with KS. Optimizing the dosing schedule will be important in the evaluation of NT-I7 in this patient population. CD4 lymphocytopenia in people living with HIV has a specific etiology and is substantially unique from other cancer populations. KS responses based on changes in CD4 counts have been established in the setting of HIV, distinguishing it from other cancers. The dosing schedule for this proposal is based on PD data from short acting IL-7 in people living with HIV and no cancer (Figure 1). In this study by Thiébaut *et. al.,* participants received weekly IL-7 for 3 weeks, had a peak CD4 count on week 4 that gradually declined over time. The CD4 count at week 4 decreased from peak but remained elevated compared to baseline. NT-I7 (IL-7-Fc) has much longer serum half-life than IL-7. The proposed schedule was suggested by NeoImmuneTech (NIT). NIT has preclinical data showing that over stimulation from too frequent dosing might have a negative effect. At present there does not appear to be a compelling rationale for more frequent dosing in HIV associated cases. This Phase I study will evaluate the kinetics of peripheral and tumor T cell expansion after the first and second doses of NT-I7. Evaluation of the safety of NT-I7 will include stopping rules for clinically significant events related to treatment of HIV (i.e., induction of HIV viremia with a drug resistant strain; clinical AIDS-defining events attributed to HIV viremia and associated immune decline despite demonstration of HIV adherence) as well as detailed evaluation of the effects on the HIV reservoir.

2.5 Correlative Studies Background

2.5.1 Pre-clinical Studies

In pre-clinical studies, NT-I7 has demonstrated potent anti-tumor efficacy, both as a monotherapy and in combination with chemo/radiotherapy and immune checkpoint inhibitors (CPIs). By increasing peripheral and tumor infiltrating lymphocytes, and increasing T cell functionality, NT-I7 synergizes with therapies such as chemotherapy, radiation, and CPIs. In a thymectomy-induced lymphopenia model (TILP) of C57BL/6MC-38-bearing mice, a combination of NT-I7 and anti-PD had significant anti-tumor effects that exceeded those of NT-I7 or anti-PD-1 therapies alone**.** The combination treatment increased intratumoral CD4+ and CD8+ T cell infiltration compared to treatment with either agent alone (Figure 4).

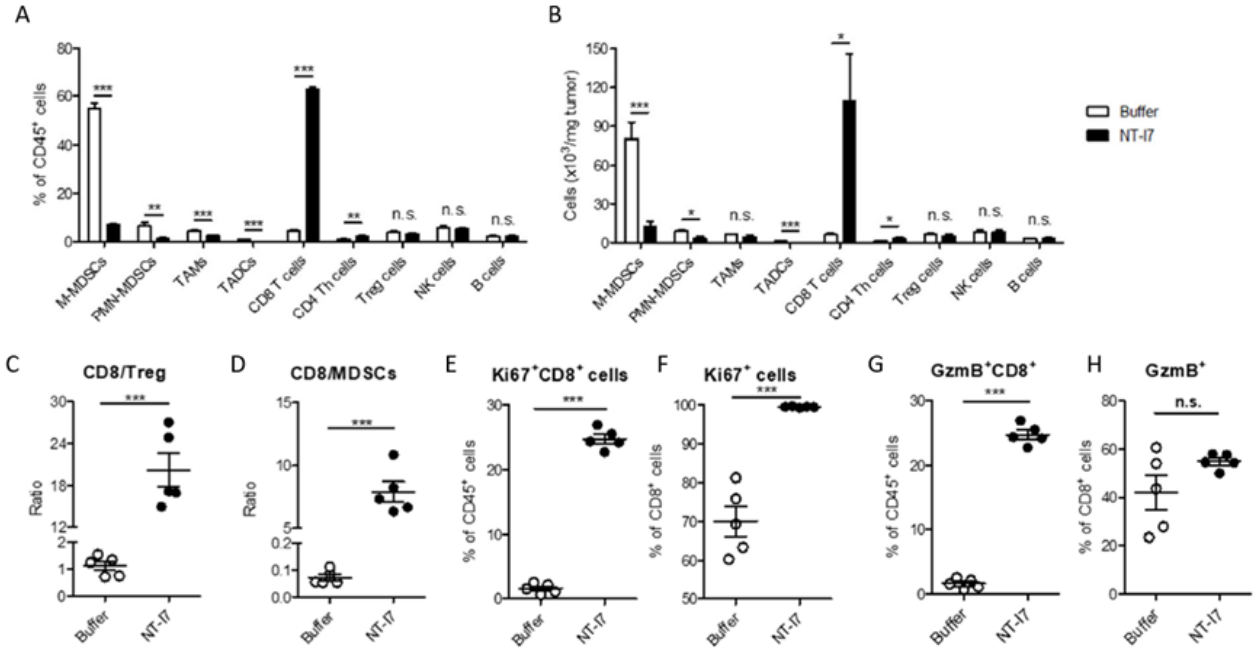


Figure 4: Synergistic anti-tumor efficacy of NT-I7 and anti-PD-1 combination therapy is associated with a greater increase in CD4+ and CD8+ T cell infiltration than in monotherapy.

NT-I7 and anti-PD-1 combination therapy is further associated with a less exhausted phenotype of CD8+ TILs, where surface expression of co-inhibitory receptors PD-1 and TIM-3 was reduced CD8+ TILs (Figure 5). A positive correlation between the number of CD8+ TILs and the suppression of tumor growth suggests that the combo therapy of NT-I7 with anti-PD-1 might increase tumor-specific cytotoxic CD8+ T cells.

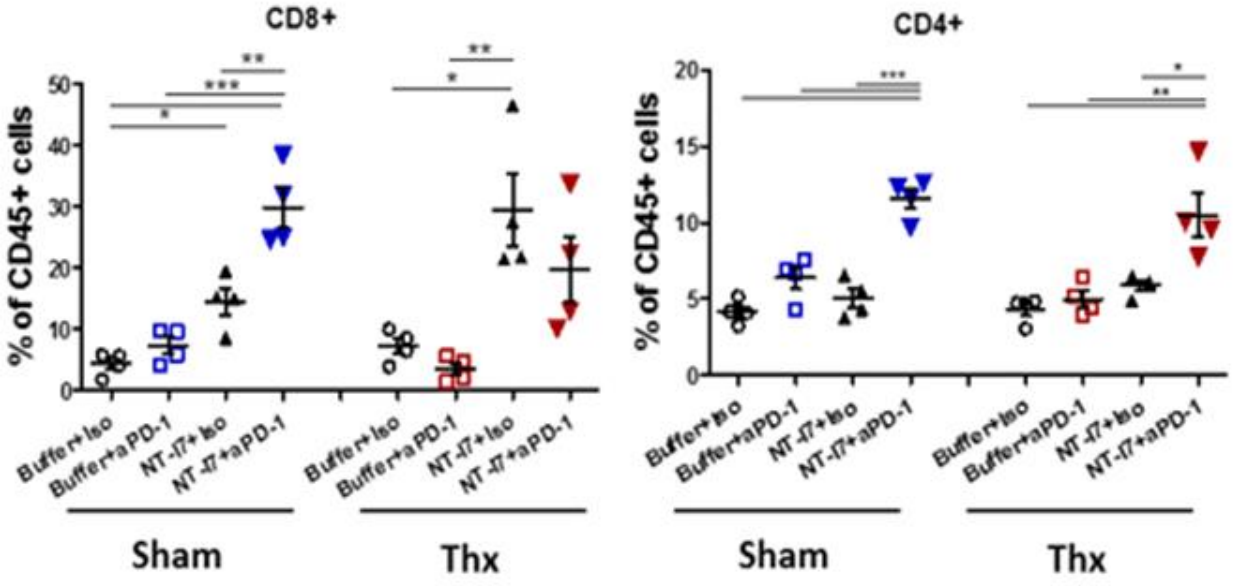


Figure 5: NT-I7 monotherapy promotes an immune-favorable tumor microenvironment (TME).

A separate experiment evaluating 10mg/kg NT-I7 as a monotherapy in an MC-38 tumor model demonstrated that administration of NT-I7 created an immune-favorable tumor microenvironment (TME) by increasing the amount of tumor-infiltrating lymphocytes (TIL), the ratio of CD8+ Ts to regulatory Ts and MDSCs in the TME, and increasing the proliferative and effector capacity of CD8+ TIL.

3. PATIENT SELECTION

3.1 Eligibility Criteria

3.1.1 Patients must have histologically confirmed Kaposi sarcoma.

3.1.2 Patients must have evaluable disease.
Note: Kaposi sarcoma will be evaluated using a modified version (consistent with NCI studies) of the AIDS Clinical Trial Group (ACTG) Oncology Committee staging and response definitions for KS.

3.1.3 No upper or lower limit on the number of prior therapies or stage of disease. No prior systemic therapy (other than ART for HIV) or local therapy is required.

3.1.4 HIV-positive patients must have been on effective anti-retroviral (ART) therapy for at least 3 months prior to enrollment, with persistent KS affecting quality of life due to

either T_1 disease or T_0 disease with inadequate disease regression on ART alone.

3.1.5 HIV-positive patients must have undetectable HIV viral loads ≤40 copies/mL measured using an FDA-approved commercial assay with lower limit of detection between ≤20 copies/mL and ≤ 40 copies/mL.

3.1.6 Patients with visceral involvement must:

- Meet other eligibility criteria
- Have any/all associated tumor associated symptoms ≤ Grade 2 by CTCAE criteria; and/or
- Require no immediate intervention (e.g., mild oozing of oral KS not an exclusion criteria)

3.1.7 Patients must provide newly obtained core, punch, or excisional biopsy of a tumor lesion obtained up to 28 days prior to treatment initiation. An archival tumor sample obtained within 1 year of screening is allowed if pre-treatment biopsy is deemed unsafe or technically not feasible.

3.1.8 Patients must be ≥18 years of age on day of signing informed consent document. Because no dosing or adverse event data are currently available on the use of NT-I7 in patients <18 years of age, children are excluded from this study but will be eligible for future pediatric trials.

3.1.9 ECOG performance status ≤2 (Karnofsky ≥60%, see Appendix A).

3.1.10 Patients must have adequate organ and marrow function as defined below:

– leukocytes	≥2,500/mcL
– absolute neutrophil count	≥1,000/mcL
– platelets	≥100,000/mcL
– hemoglobin	≥9/dL
– total bilirubin	≤ 1.5 institutional upper limit of normal (ULN) OR <3 x institutional ULN for Gilbert's syndrome or HIV protease inhibitors
– AST(SGOT)/ALT(SGPT)	≤2.5 × institutional ULN
– creatinine	≤ 2 x institutional ULN OR
– creatinine clearance	≥60 mL/min/1.73 m^2 by Cockroft-Gault: $\frac{(140 - \text{age}) \times (\text{weight in kg}) \times (0.85 \text{ if female})}{72 \times (\text{serum creatinine in mg/dL})}$

At the discretion of the treating physician, a 24-hour urine creatinine clearance could be obtained and utilized as the gold standard if creatinine clearance by Cockcroft-Gault is <30 and prevents patient enrollment on the trial.

3.1.11 Patients with chronic hepatitis B virus (HBV) infection must be on suppressive antiviral therapy.

3.1.12 Patients with a history of hepatitis C virus (HCV) infection must have an undetectable HCV viral load due to prior treatment or natural resolution.

3.1.13 Female patients of childbearing potential must have a negative urine or serum pregnancy test within 72 hours before receiving the first dose of the study agent. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

3.1.14 The effects of NT-I7 on the developing human fetus are unknown. For this reason and because NT-I7 may have an adverse effect on pregnancy and poses risk to the human fetus, 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 for 90 days after the last dose of study treatment. 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. Men treated or enrolled on this protocol must also agree to use adequate contraception prior to the study, for the duration of study participation, and for 90 days after completion of NT-I7 administration.

3.1.15 Ability to understand and the willingness to sign a written informed consent document.

3.1.16 Patients with impaired decision-making capacity will not be excluded.

3.2 Exclusion Criteria

3.2.1 Patients who have had chemotherapy, radiotherapy or other KS directed therapy other than ART for HIV within 2 weeks before the initiation of study treatment.

3.2.2 Patients who have not recovered from immune related adverse events due to prior therapy (*i.e.*, have residual toxicities > Grade 1) with the exception of hypothyroidism managed by supplemental levothyroxine.

3.2.3 Patients who have received treatment with any other investigational agent within 4 weeks before initiation of study treatment.

3.2.4 Patients with known hypersensitivity to Chinese hamster ovary cell products or other recombinant human antibodies.

3.2.5 Patients who have a history of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins.

3.2.6 Patients who have received treatment with systemic immunostimulatory agents

(including, but not limited to, interferon [IFN]-α or interleukin [IL]-2, pomalidomide, or immune checkpoint inhibitors) within 6 weeks before initiation of study treatment.

3.2.7 Patients who have received treatment with systemic immunosuppressive medications (including, but not limited to, prednisone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and antitumor necrosis factor [anti-TNF] agents) within 2 weeks before initiation of study treatment.

- Patients who have received acute, low dose, systemic immunosuppressant medications (e.g., a one-time dose of dexamethasone for nausea) may be enrolled.
- The use of inhaled corticosteroids, and mineralocorticoids (e.g., fludrocortisone) for patients with orthostatic hypotension or adrenocortical insufficiency is allowed.

3.2.8 Patients who have a history or risk of autoimmune disease, including, but not limited to, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener's granulomatosis, Sjögren's syndrome, Bell's palsy, Guillain-Barré syndrome, multiple sclerosis, autoimmune thyroid disease, vasculitis, or glomerulonephritis.

Note: the following will NOT be exclusionary:

- The presence of laboratory evidence of autoimmune disease (e.g., positive antinuclear antibody (ANA) titer or lupus anticoagulant) without associated symptoms
- Clinical evidence of vitiligo or other forms of depigmenting illness
- Mild autoimmunity not impacting the function of major organs (e.g., limited psoriasis)

3.2.9 Patients with uncontrolled intercurrent illness including, but not limited to, symptomatic congestive heart failure (New York Heart Association Class III or IV), unstable angina pectoris, cardiac arrhythmia, recent myocardial infarction (within the last 6 months). Patients with known history of treatment with cardiotoxic agents, including anthracyclines, should have a clinical risk assessment of cardiac function using the New York Heart Association Functional Classification.

3.2.10 Psychiatric illness/social situations that would limit compliance with study requirements.

3.2.11 Pregnant women are excluded from this study because the effects of NT-I7 on the developing human fetus are unknown. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with NT-I7, breastfeeding should be discontinued if the mother is treated with NT-I7.

3.2.12 Patients with a history of solid organ or allogeneic stem cell transplant.

3.2.13 Patients with continuing KS regression on ART alone. Stable disease allowed.

3.2.14 Patients with a prior or concurrent malignancy requiring active therapy.

3.2.15 Patients with active tuberculosis.

3.2.16 Patients who have a history of idiopathic pulmonary fibrosis, pneumonitis (including drug induced), organizing pneumonia (bronchiolitis obliterans, cryptogenic organizing pneumonia, etc.), or evidence of active pneumonitis on screening chest X-Ray. History of radiation pneumonitis in the radiation field (fibrosis) is permitted.

3.3 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial.

4. REGISTRATION PROCEDURES

4.1 Investigator and Research Associate Registration with CTEP

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account at https://ctepcore.nci.nih.gov/iam. In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) at https://ctepcore.nci.nih.gov/rcr.

RCR utilizes five person registration types.

- IVR – MD, DO, or international equivalent;
- NPIVR – advanced practice providers (e.g., NP or PA) or graduate level researchers (e.g., PhD);
- AP – clinical site staff (e.g., RN or CRA) with data entry access to CTSU applications such as the Roster Update Management [RUMS], OPEN, Rave, acting as a primary site contact, or with consenting privileges;
- Associate (A): other clinical site staff involved in the conduct of NCI-sponsored trials, and
- Associate Basic (AB): individuals (e.g., pharmaceutical company employees) with limited access to NCI-supported systems.

Documentation Required	IVR	NPI VR	AP	A	AB
FDA Form 1572	✓	✓			
Financial Disclosure Form	✓	✓	✓		
NCI Biosketch (education, training, employment, license, and certification)	✓	✓	✓		
GCP training	✓	✓	✓		
Agent Shipment Form (if applicable)	✓				
CV (optional)	✓	✓	✓		

RCR requires the following registration documents:

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and Cancer Trials Support Unit (CTSU) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and Institutional Review Boards (IRBs) covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Addition to a site roster,
- Assign the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN,
- Act as the site-protocol Principal Investigator (PI) on the IRB approval, and
- Assign the Clinical Investigator (CI) role on the Delegation of Tasks Log (DTL).

In addition, all investigators acting as the Site-Protocol PI (investigator listed on the IRB approval), consenting/treating/drug shipment investigator in OPEN, or as the CI on the DTL must be rostered at the enrolling site with a participating organization.

Additional information is located on the CTEP website at https://ctep.cancer.gov/investigatorResources/default.htm. For questions, please contact the **RCR Help Desk** by email at RCRHelpDesk@nih.gov.

4.2 Site Registration

Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU Regulatory Support System (RSS).

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

IRB Approval

For CTEP and Division of Cancer Prevention (DCP) studies open to the National Clinical Trials Network (NCTN) and NCI Community Oncology Research Program (NCORP) Research Bases after March 1, 2019, all U.S.-based sites must be members of the NCI Central Institutional

Review Board (NCI CIRB). In addition, U.S.-based sites must accept the NCI CIRB review to activate new studies at the site after March 1, 2019. Local IRB review will continue to be accepted for studies that are not reviewed by the CIRB, or if the study was previously open at the site under the local IRB. International sites should continue to submit Research Ethics Board (REB) approval to the CTSU Regulatory Office following country-specific regulations.

Sites participating with the NCI CIRB must submit the Study Specific Worksheet (SSW) for Local Context to the CIRB using IRB Manager to indicate their intent to open the study locally. The NCI CIRB's approval of the SSW is automatically communicated to the CTSU Regulatory Office, but sites are required to contact the CTSU Regulatory Office at CTSURegPref@ctsu.coccg.org to establish site preferences for applying NCI CIRB approvals across their Signatory Network. Site preferences can be set at the network or protocol level. Questions about establishing site preferences can be addressed to the CTSU Regulatory Office by email or calling 1-888-651-CTSU (2878).

In addition, the Site-Protocol Principal Investigator (PI) (*i.e.*, the investigator on the IRB/REB approval) must meet the following five criteria in order for the processing of the IRB/REB approval record to be completed:

- Holds an Active CTEP status;
- Active status at the site(s) on the IRB/REB approval (*applies to US and Canadian sites only*) on at least one participating organization's roster;
- If using NCI CIRB, active on the NCI CIRB roster under the applicable CIRB Signatory Institution(s) record;
- Includes the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile;
- Lists all sites on the IRB/REB approval as Practice Sites in the Form FDA 1572 in the RCR profile; and
- Holds the appropriate CTEP registration type for the protocol.

Additional Requirements

Additional site requirements to obtain an approved site registration status include:

- An active Federalwide Assurance (FWA) number;
- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO);
- An active roster affiliation with the NCI CIRB roster under at least one CIRB Signatory Institution (US sites only); and
- Compliance with all protocol-specific requirements (PSRs).

4.2.1 Downloading Regulatory Documents

Download the site registration forms from the protocol-specific page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted to institutions and its associated investigators and staff on a participating roster. To

view/download site registration forms:

- Log on to the CTSU members' website (https://www.ctsu.org) using your CTEP-IAM username and password;
- Click on the *Protocols* tab in the upper left of your screen:
  - Enter the protocol number in the search field at the top of the protocol tree, or
  - Click on the By Lead Organization folder to expand, then select CITN, and protocol number CITN-17.
- Click on *Documents*, *Protocol Related Documents*, and use the *Document Type* filter and select *Site Registration* to download and complete the forms provided. (Note: For sites under the CIRB initiative, IRB data will load automatically to the CTSU.)

4.2.2 Submitting Regulatory Documents

Submit required forms and documents to the CTSU Regulatory Office using the Regulatory Submission Portal on the CTSU members' website.

To access the Regulatory Submission Portal, log in to the CTSU members' website, go to the *Regulatory* section and select *Regulatory Submission*.

Institutions with patients waiting that are unable to use the Regulatory Submission Portal should alert the CTSU Regulatory Office immediately by phone or email: 1-866-651- CTSU (2878), or CTSURegHelp@coccg.org in order to receive further instruction and support.

Delegation of Tasks Log (DTL)

Each site must complete a protocol-specific Delegation of Tasks Log (DTL) using the DTL application in the Delegation Log section on the CTSU members' website. The Clinical Investigator (CI) is required to review and electronically sign the DTL prior to the site receiving an Approved site registration status and enrolling patients to the study. To maintain an approved site registration status, the CI must re-sign the DTL at least annually and when a new version of the DTL is released; and to activate new task assignments requiring CI sign-off. Any individual at the enrolling site on a participating roster may initiate the site DTL. Once the DTL is submitted for CI approval, only the designated DTL Administrators or the CI may update the DTL. Instructions on completing the DTL are available in the Help Topics button in the DTL application and include a Master Task List, which describes DTL task assignments, CI signature, and CTEP registration requirements.

4.2.3 Checking Site Registration Status

Site registration status may be verified on the CTSU members' website.

- Click on *Regulatory* at the top of the screen;
- Click on *Site Registration;* and
- Enter the sites 5-character CTEP Institution Code and click on Go:
    - Additional filters are available to sort by Protocol, Registration Status, Protocol Status, and/or IRB Type.

Note: The status shown only reflects institutional compliance with site registration requirements as outlined above. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

4.3 Patient Registration

4.3.1 OPEN / IWRS

The Oncology Patient Enrollment Network (OPEN) is a web-based registration system available on a 24/7 basis. OPEN is integrated with CTSU regulatory and roster data and with the Lead Protocol Organization (LPOs) registration/randomization systems or Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. OPEN will populate the patient enrollment data in NCI's clinical data management system, Medidata Rave.

Requirements for OPEN access:

- A valid CTEP-IAM account;
- To perform enrollments or request slot reservations: Be on an LPO roster, ETCTN Corresponding roster, or Participating Organization roster with the role of Registrar. Registrars must hold a minimum of an AP registration type;
- If a Delegation of Tasks Log (DTL) is required for the study, the registrar(s) must hold the OPEN Registrar task on the DTL for the site; and
- Have an approved site registration for a protocol prior to patient enrollment.

To assign an Investigator (IVR) or Non-Physician Investigator (NPIVR) as the treating, crediting, consenting, drug shipment (IVR only), or receiving investigator for a patient transfer in OPEN, the IVR or NPIVR must list the IRB number used on the site's IRB approval on their Form FDA 1572 in RCR. If a DTL is required for the study, the IVR or NPIVR must be assigned the appropriate OPEN-related tasks on the DTL.

Prior to accessing OPEN, site staff should verify the following:

- Patient has met all eligibility criteria within the protocol stated timeframes; and
- All patients have signed an appropriate consent form and Health Insurance Portability and Accountability (HIPAA) authorization form (if applicable).

Note: The OPEN system will provide the site with a printable confirmation of registration and

treatment information. Please print this confirmation for your records.

Access OPEN at https://open.ctsu.org or from the OPEN link on the CTSU members' website. Further instructional information is in the OPEN section of the CTSU website at https://www.ctsu.org or https://open.ctsu.org. For any additional questions, contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

Patient enrollment for this study will be facilitated using the Slot Reservation System in conjunction with the registration system in OPEN. Prior to discussing protocol entry with the patient, all site staff must use the CTSU OPEN Slot Reservation System to ensure that a slot on the protocol is available to the patient. Once a slot reservation confirmation is obtained, site staff may then proceed to enroll the patient to this study.

4.3.2 OPEN/IWRS Questions?

Further instructional information on OPEN is provided on the OPEN tab of the CTSU website at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

Theradex has developed a Slot Reservations and Cohort Management User Guide, which is available on the Theradex website: http://www.theradex.com/clinicalTechnologies/?National-Cancer-Institute-NCI-11. This link to the Theradex website is also on the CTSU website OPEN tab. For questions about the use of IWRS for slot reservations, contact the Theradex Helpdesk at 609-619-7862 or Theradex main number 609-799-7580; CTMSSupport@theradex.com.

4.4 General Guidelines

Following registration, patients should begin protocol treatment within 5 business days. Issues that would cause treatment delays should be discussed with the PI. If a patient does not receive protocol therapy following registration, the patient's registration on the study may be canceled. The Clinical Research Site (CRS) must notify the CITN Coordinating Center of cancellations as soon as possible.

5. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

5.1 Summary Table for Specimen Collection

Table 3. Specimen Collection Summary

Time Point	Specimen	Send Specimens To:
Archival[1]		
	• Formalin-fixed, paraffin-embedded tumor blocks (preferred) or FFPE slides (if blocks are unavailable) (mandatory)[1]	CIML
Baseline (Week 0)		
	• Tissue in formalin (mandatory)[1] • 7 ml blood in SST (mandatory) (ADA/NADA) • 2 x 7 ml blood in SST (mandatory) (PK) • 8.5 ml blood in ACD (mandatory) (TCRSeq) • 17 ml blood in ACD (mandatory) (Viral Load) • 17 ml blood in ACD (optional) (Flow, Cytokines, IL7) • 68 ml blood in ACD (optional) (KSHV T cell Resp) • 8.5 ml blood in ACD (optional) (KSHV Humoral)	CIML
	• 6 mL blood in EDTA (mandatory) (CBC, CD4+ and CD8+ T cell counts)	CLIA Certified Laboratory
Week 1		
	• 17 ml blood in ACD (optional) (Flow) • 7 ml blood in SST (mandatory) (PK)	CIML
	• 6 mL blood in EDTA (mandatory) (CBC, CD4+ and CD8+ T cell counts)	CLIA Certified Laboratory
Week 4		
	• 17 ml blood in ACD (mandatory) (Viral Load) • 8.5 ml blood in ACD (mandatory) (TCRSeq) • 17 ml blood in ACD (optional) (Flow, Cytokines, IL7) • 8.5 ml blood in ACD (optional) (KSHV Humoral)	CIML
	• 6 mL blood in EDTA (mandatory) (CBC, CD4+ and CD8+ T cell counts)	CLIA Certified Laboratory
Week 9		
	• Tissue in formalin (mandatory)[2] • 17 ml blood in ACD (mandatory) (Viral Load) • 8.5 ml blood in ACD (optional) (KSHV Humoral) • 68 ml blood in ACD (optional) (KSHV T cell Resp) • 7 ml blood in SST (mandatory) (ADA/NADA) • 2 x 7 ml blood in SST (mandatory) (PK) • 8.5 ml blood in ACD (mandatory) (TCRSeq) • 17 ml blood in ACD (optional) (Flow, Cytokines, IL7)	CIML
	• 6 mL blood in EDTA (mandatory) (CBC, CD4+ and CD8+ T cell counts)	CLIA Certified Laboratory

Week 13		
	• Tissue in formalin (optional) • 17 ml blood in ACD (optional) (Flow)	CIML
	• 6 mL blood in EDTA (mandatory) (CBC, CD4+ and CD8+ T cell counts)	CLIA Certified Laboratory
Week 18		
	• 7 ml blood in SST (mandatory) (ADA/NADA) • 2 x 7 ml blood in SST (mandatory) (PK) • 8.5 ml blood in ACD (mandatory) (TCRSeq) • 17 ml blood in ACD (optional) (Flow, Cytokines, IL7)	CIML
	• 6 mL blood in EDTA (mandatory) (CBC, CD4+ and CD8+ T cell counts)	CLIA Certified Laboratory
Week 27		
	• 7 ml blood in SST (mandatory) (ADA/NADA) • 2 x 7 ml blood in SST (mandatory) (PK) • 8.5 ml blood in ACD (mandatory) (TCRSeq, Cytokines, IL7)	CIML
End of Treatment		
	• 7 ml blood in SST (mandatory) (ADA/NADA) • 7 ml blood in SST (mandatory) (PK) • 17 ml blood in ACD (mandatory) (Viral Load) • 68 ml blood in ACD (optional) (KSHV T cell Resp) • 8.5 ml blood in ACD (optional) (KSHV Humoral) • Tissue in formalin (mandatory)[2]	CIML

[1] Baseline tumor biopsy (fresh) may be obtained up to 28 days prior to treatment initiation. An archival tumor sample obtained within 1 year of screening is allowed if the pre-treatment biopsy is deemed unsafe or technically not feasible.
[2] Post-treatment tumor biopsy will be obtained prior to dosing on Cycle 2, Week 9, Day 1 or at the End of Treatment visit, whichever occurs first.

5.2 Summary Table(s) for Research Biopsies

Table 4. Mandatory Biopsy #1 Collection Summary.

Biopsy #: 1 (Mandatory)				
Trial Time Point: Baseline				
Biopsy Definition: Research – No Clinical Impact (All cores from a single biopsy procedure impact research goals, but do not directly impact patient care or benefit the patient.)				
Core Priority	**Use in the Trial**	**Biomarker Name(s)**	**Tumor Content Required**	**Post-Biopsy Processing**
1	Integrated	TCR Clonality	[5-25% or greater]	Formalin
2	Exploratory	CD3, CD8, CD4, CD79A CD68, PD-1, FoxP3 and MHC Class I	[5-25% or greater]	Formalin
1	Exploratory	Gene Expression Profiling	[5-25% or greater]	Formalin

Table 5. Mandatory Biopsy #2 Collection Summary.

Biopsy #: 2 (Mandatory)				
Trial Time Point: 9 weeks (Post-treatment tumor biopsy will be obtained prior to dosing on Cycle 2, Week 9, Day 1 or at the End of Treatment visit, whichever occurs first.)				
Biopsy Definition: Research – No Clinical Impact (All cores from a single biopsy procedure impact research goals, but do not directly impact patient care or benefit the patient.)				
Core Priority	**Use in the Trial**	**Biomarker Name(s)**	**Tumor Content Required**	**Post-Biopsy Processing**
1	Integrated	TCR Clonality	[5-25% or greater]	Formalin
2	Exploratory	CD3, CD8, CD4, CD79A CD68, PD-1, FoxP3 and MHC Class I	[5-25% or greater]	Formalin
1	Exploratory	Gene Expression Profiling	[5-25% or greater]	Formalin

Table 6. Optional Biopsy #1 Collection Summary.

Biopsy #: 1 (Optional)				
Trial Time Point: 13 weeks (4 weeks after second dose)				
Biopsy Definition: Research – No Clinical Impact (All cores from a single biopsy procedure impact research goals, but do not directly impact patient care or benefit the patient.)				
Core Priority	**Use in the Trial**	**Biomarker Name(s)**	**Tumor Content Required**	**Post-Biopsy Processing**
1	Integrated	TCR Clonality	[5-25% or greater]	Formalin
2	Exploratory	CD3, CD8, CD4, CD79A CD68, PD-1, FoxP3 and MHC Class I	[5-25% or greater]	Formalin

5.3 Specimen Procurement Kits and Scheduling

5.3.1 Specimen Collection Kits

Specimens will be collected for several planned correlative studies. Many samples will be processed and stored to be run in batches. The CITN Immune Monitoring Laboratory will provide lab kits and shipping supplies. Specific instructions on numbers and types of tubes required for each visit are provided in the CITN-17 Laboratory Manual.

When blood volume or specimen material is limited, the correlative studies will be considered secondary to tests needed to make clinical decisions. Prioritization of secondary tests will be made based on technical considerations, total amount of sample from each individual subject, total number of samples acquired, total number of each assay performed, and information gained from the assays performed to date. The anticipated priority correlatives in order of importance, are noted in Section 5.5, Table 7.

5.4 N/A

5.5 Biomarker plan

Table 7. List of Biomarker Assays in Order of Priority

Priority	Biomarker Name	Assay (CLIA: Y/N)	Use in the Trial and Purpose	Specimens Tested	Collection Time Points	Mandatory (M) or Optional (O)	Assay Laboratory
Tissue-based Biomarkers							
1	TCR Clonality	ImmunoSeq CLIA: N	Integrated Pharmacodynamics	KS biopsies	Baseline (week 0), week 9 or EOT, additional time point at week 13 is optional.	M (W0; W9 or EOT) O (W13)	Adaptive Biotechnologies
1	CD3, CD8, CD4, CD79A CD68, PD-1, FoxP3 and MHC Class I	Multi-Spectral IHC CLIA: N	Exploratory Pharmacodynamics	KS biopsies	Baseline (week 0), week 9 or EOT, additional time point at week 13 is optional.	M (W0; W9 or EOT) O (W13)	Fred Hutch Experimental Pathology
1	Gene Expression Profiling Interferon γ (INFγ) Gene Expression Signature	Nanostring nCounter® PanCancer ThePanCancer IO 360™ Additional add-in probes for genes that define the KSHV function CLIA: N	Exploratory Pharmacodynamics	KS biopsies	Baseline (week 0), week 9 or EOT	M	Fred Hutch Molecular Core and Collaboration with NanoString® Technologies

Priority	Biomarker Name	Assay (CLIA: Y/N)	Use in the Trial and Purpose	Specimens Tested	Collection Time Points	Mandatory or Optional	Assay Laboratory a
Blood-based Biomarkers							
1	Absolute lymphocyte count	CBC CLIA: Y	Integral Dosing considerations	PBMC (EDTA)	Baseline (week 0), week 1, week 4, week 9 (before second dose), week 13, week 18	M	CLIA Certified Site Laboratory
2	CD4+ and CD8+ T-cell counts	Flow Cytometry CLIA: Y	Integrated Pharmacodynamics	PBMC	Baseline (week 0), week 1, weeks 4, week 9 (before second dose), week 18, week 27	M	CLIA Certified Site Laboratory
1	ADA and NADA	ELISA CLIA: N	Integrated Dosing Considerations	Serum	Baseline (week 0), week 9; week 18; week 27; EOT	M	BioAgilytix
2	Whole Blood Immunophenotyping	Flow Cytometry CLIA: N	Exploratory Pharmacodynamics	Whole blood and PBMC	Baseline (week 0), week 1, week 4, week 9 (before second dose), week 18, week 27	O	CITN Central Immune Monitoring Lab (CIML) Steve Fling Sfling@fredhutch.org

Priority	Biomarker Name	Assay (CLIA: Y/N)	Use in the Trial and Purpose	Specimens Tested	Collection Time Points	Mandatory or Optional	Assay Laboratory a
Blood-based Biomarkers (cont.)							
2	KSHV Humoral Response	Luminex CLIA: N	Exploratory Correlate of response	Plasma	Baseline (week 0), week 4, week 9, EOT	O	Viral Oncology Section, Frederick National Laboratory for Cancer Research Denise Whitby whitbyd@mail.nih.gov
1	KSHV PBMC Viral Load	PCR CLIA: Y	Integrated Viral Correlate	PBMC	Baseline (week 0), week 4, week 9, EOT	M	Viral Oncology Section, Frederick National Laboratory for Cancer Research Denise Whitby whitbyd@mail.nih.gov
2	Anti-KSHV Immune T-cell Response	Multiplex ELISPOT CLIA: N	Exploratory Immune Correlate	PBMC	Baseline (week 0), week 9, EOT	O	Viral Oncology Section, Frederick National Laboratory for Cancer Research Denise Whitby whitbyd@mail.nih.gov
1	TCR Clonality	ImmunoSeq CLIA: N	Integrated Pharmacodynamics	PBMC	Baseline (week 0), week 4, week 9, week 18, week 27	M	Adaptive Biotechnologies
2	IL-7/Cytokines	ELISA CLIA: N	Exploratory Pharmacokinetics	Plasma	Baseline (week 0), week 4, week 9, week 18, week 27	O	Fred Hutch Shared Resources
1	NT-I7 PK	LC-MS CLIA: N	Integrated Pharmacodynamics	Serum	Baseline (week 0), week 1, week 9, week 18, week 27, EOT	M	BioAgilytix

5.6 Integral Correlative Studies

5.6.1 *Absolute Lymphocyte Count – Integral Laboratory Study #1*

5.6.1.1 Collection of Specimen(s)
Blood draws will be performed by venipuncture on study subjects in EDTA or other blood draw tubes as specified per local site SOP.

5.6.1.2 Handling of Specimen(s)
Blood Samples will be collected at room temperature and shipped ambient to the local clinical lab.

5.6.1.3 Shipping of Specimen(s)
Blood collection tubes will be shipped at ambient temperature to the designated local clinical, CLIA compliant laboratory the same day as the blood draw.

5.6.1.4 Site(s) Performing Correlative Study
Assays will be performed at each local clinical site. Assays are to be performed at each site by a CLIA compliant laboratory. The specific technique is not specified in the protocol.

5.7 Integrated Correlative Studies

5.7.1 *T-Cell Receptor Repertoire Analysis – TCR sequencing - Integrated Laboratory Correlative Study #1*

5.7.1.1 Collection of Specimen(s)
Specimens will include archived and prospectively obtained tumor biopsies and blood samples. Blood draws will be performed by venipuncture.

5.7.1.2 Handling of Specimen(s)
Biopsy samples will be placed in formalin and shipped to the CIML. Blood collection tubes will be shipped on day of blood draw for overnight delivery to the CIML.

5.7.1.3 Shipping of Specimen(s)
Whole blood and biopsies in formalin will be shipped ambient to the CIML. Blood will be processed to PBMC as described above. Clinical sites will utilize a web-based specimen system (BSI-Engage) to communicate with the CIML. The CIML will coordinate shipment of samples to Adaptive Biosciences.

5.7.1.4 Site(s) Performing Correlative Study
Samples will be analyzed at Adaptive Bioscience in Seattle, WA, or other agreed upon vendor or collaborator.

5.7.2 *Evaluation of peripheral CD4+ and CD8+ T-cell counts – Integrated Laboratory Correlative Study #2*

5.7.2.1 Collection of Specimen(s)
Blood draws will be performed by venipuncture on study subjects in EDTA or other blood draw tubes as specified per local site SOP.

5.7.2.2 Handling of Specimen(s)
Blood Samples will be collected at room temperature and shipped ambient to the local clinical lab.

5.7.2.3 Shipping of Specimen(s)
Blood collection tubes will be shipped at ambient temperature to the designated local clinical, CLIA compliant laboratory the same day as the blood draw.

5.7.2.4 Site(s) Performing Correlative Study
Assays will be performed at each local clinical site. Assays are to be performed at each site by a CLIA compliant laboratory. The specific technique is not specified in the protocol.

5.7.3 *KSHV Viral Load Analysis – Integrated Laboratory Correlative Study #4*

5.7.3.1 Collection of Specimen(s)
Blood draws will be performed by venipuncture on study subjects prior to NT-I7 injection when scheduled on the same day as NT-I7 administration.

5.7.3.2 Handling of Specimen(s)
Blood collection tubes (for subsequent PBMC isolation) will be shipped on day of blood draw for overnight delivery to the CIML.

5.7.3.3 Shipping of Specimen(s)
Blood collection tubes will be shipped overnight at ambient temperature to the CIML using CIML established SOPs. Clinical sites will utilize a web-based specimen system (BSI-Engage) to communicate with the CIML. The CIML will coordinate shipment via cryoport of cryopreserved PBMC.

5.7.3.4 Site(s) Performing Correlative Study
Batched samples will be analyzed at the Frederick National Laboratory for Cancer Research at the end of the study.

5.8 Exploratory Correlative Studies

5.8.1 *Assessment of tumor biopsy by gene expression analysis -- Interferon γ (INFγ) Gene Expression Signature - NanoString® nCounter® Human Immunology V2 Panel and the nCounter® PanCancer Immune Profiling Panel - Exploratory Laboratory Correlative*

Study #1

5.8.1.1 Collection of Specimen(s)
Patients will undergo a pre-treatment biopsy and a post-treatment biopsy (core, punch, or excisional) as part of this protocol if it is deemed relatively safe and technically feasible. Alternatively, formalin-fixed, paraffin-embedded archival tissue block(s) from tumor obtained within 1 year from the screening visit will be identified by the clinical site at the relevant pathology laboratories where they were processed and stored.

5.8.1.2 Handling of Specimen(s)
Biopsy samples will be placed in formalin and shipped for overnight delivery to the CIML.

5.8.1.3 Shipping of Specimen(s)
For archival samples, clinical sites will arrange for the formalin-fixed, paraffin-embedded tumor blocks (preferred) or FFPE slides (if blocks are unavailable) to be shipped at ambient temperature to the CIML. For biopsies done as part of this protocol, tissue in formalin will be shipped overnight at ambient temperature to the CIML. Clinical sites will utilize a web-based specimen system (BSI-Engage) to communicate with the CIML. After sectioning at the CIML, the CIML will coordinate shipment of unstained slides (or RNA) to NanoString®. Depending on the specific contract, RNA will be extracted from FFPE slides, either at NanoString® or the CIML, using established protocols (MAN-10050-02 Preparing Nucleic Acid from FFPE Samples for Use with nCounter® Assays).

5.8.1.4 Site(s) Performing Correlative Study
Assays will be performed by NanoString® Technologies in Seattle, WA, and analyzed using qualified analytic tools at the Fred Hutch.

5.8.2 *Antitumor Immune T-cell Response – KSHV ELISPOT – Exploratory Laboratory Correlative Study #2*

5.8.2.1 Collection of Specimen(s)
Blood draws will be performed by venipuncture on study subjects just before, during, and at end of treatment.

5.8.2.2 Handling of Specimen(s)
Blood collection tubes (for subsequent PBMC and plasma isolation) will be shipped on day of blood draw for overnight delivery to the CIML.

5.8.2.3 Shipping of Specimen(s)
Blood collection tubes will be shipped overnight at ambient temperature to the CIML using CIML established SOPs. Clinical sites will utilize a web-based specimen system (BSI-Engage) to communicate with the CIML. The CIML will coordinate shipment via cryoport of cryopreserved PBMC.

5.8.2.4 Site(s) Performing Correlative Study
Batched samples will be analyzed at the Frederick National Laboratory for Cancer Research at the end of the study.

5.8.3 *Multispectral IHC – Exploratory Laboratory Correlative Study #3*

5.8.3.1 Collection of Specimen(s)
Patients will undergo a pre-treatment biopsy and a post-treatment biopsy (core, punch, or excisional) as part of this protocol if it is deemed relatively safe and technically feasible. Alternatively, formalin-fixed, paraffin-embedded archival tissue block(s) from tumor obtained within 1 years from the screening visit will be identified by the clinical site at the relevant pathology laboratories where they were processed and stored.

5.8.3.2 Handling of Specimen(s)
Biopsy samples will be placed in formalin and shipped to the CIML. Blood collection tubes will be shipped on day of blood draw for overnight delivery to the CIML.

5.8.3.3 Shipping of Specimen(s)
For archival samples, clinical sites will arrange for the formalin-fixed, paraffin-embedded tumor blocks (preferred) or FFPE slides (if blocks are unavailable) to be shipped at ambient temperature to the CIML. For biopsies done as part of this protocol, tissue in formalin will be shipped overnight at ambient temperature to the CIML. Clinical sites will utilize a web-based specimen system (BSI-Engage) to communicate with the CIML.

5.8.3.4 Site(s) Performing Correlative Study
These analyses will be performed in the CIML at the Fred Hutch or an agreed upon vendor or collaborator.

5.8.4 *Whole Blood Immunophenotyping – Exploratory Laboratory Correlative Study #4*

5.8.4.1 Collection of Specimen(s)
Blood draws will be performed by venipuncture on study subjects just before, during, and at end of treatment.

5.8.4.2 Handling of Specimen(s)
Blood collection tubes (for subsequent PBMC and plasma isolation) will be shipped on day of blood draw for overnight delivery to the CIML.

5.8.4.3 Shipping of Specimen(s)
Blood collection tubes will be shipped overnight at ambient temperature to the CIML using CIML established SOPs. Clinical sites will utilize a web-based specimen system (BSI-Engage) to communicate with the CIML.

5.8.4.4 Site(s) Performing Correlative Study
These analyses will be performed in the CIML at the Fred Hutch.

5.8.5 *KSHV Humoral Response – Exploratory Laboratory Correlative Study #5*

5.8.5.1 Collection of Specimen(s)
Blood draws will be performed by venipuncture on study subjects. The collection will take place before NT-I7 injection when scheduled on the same day as NT-I7 administration.

5.8.5.2 Handling of Specimen(s)
Blood collection tubes (for subsequent PBMC and plasma isolation) will be shipped on day of blood draw for overnight delivery to the CIML.

5.8.5.3 Shipping of Specimen(s)
Blood collection tubes will be shipped overnight at ambient temperature to the CIML using CIML established SOPs. Clinical sites will utilize a web-based specimen system (BSI-Engage) to communicate with the CIML. The CIML will coordinate shipments of serum, as needed.

5.8.5.4 Site(s) Performing Correlative Study
Batched samples will be analyzed at the Frederick National Laboratory for Cancer Research at the end of the study.

5.9 Special Studies

5.9.1 *Immunogenicity Testing*
The formation of anti-drug antibodies and neutralizing anti-drug antibodies to NT-I7 will be evaluated before the first dose of NT-I7, and then again on time points described in Table 3.

5.9.1.1 Collection of Specimen(s)
Blood draws will be performed by venipuncture on study subjects before, during and at end of treatment.

5.9.1.2 Handling of Specimen(s)
Sera will be isolated by the local laboratory and frozen at -80C.

5.9.1.3 Shipping of Specimen(s)
Serum samples will be batch shipped overnight on dry ice to the CIML (Seattle, WA). Sites will utilize a web-based specimen system (BSI-Engage) to communicate with the CIML. The CIML will coordinate the shipment of samples to the agreed upon collaborator or vendor.

5.9.1.4 Site(s) Peforming Immunogenicity Testing
Samples will be analyzed at BioAgilytix.

5.9.2 *NT-I7 Pharmacokinetics*

The pharmacokinetic profile of NT-I7 will be assessed to determine if any NT-I7 levels are affected by any ADA that may be observed. The samples will be collected before the first dose of NT-I7 and then again time points described in Table 3. Two PK blood draws for the time points (week 0, week 9, week 18, and week 27) should be performed as follows: 1) a 7 ml draw prior to NT-I7 administration; and 2) a 7 ml draw 3 hr (+/-15min) post NT-I7 administration. Only one PK blood draw is to be performed at week 1 and EOT.

5.9.2.1 Collection of Specimen(s)
Blood draws will be performed by venipuncture on study subjects before and during study treatment.

5.9.2.2 Handling of Specimen(s)
Sera will be isolated by the local laboratory and frozen at -80C.

5.9.2.3 Shipping of Specimen(s)
Serum samples will be batch shipped overnight on dry ice to the CIML (Seattle, WA). Sites will utilize a web-based specimen system (BSI-Engage) to communicate with the CIML. The CIML will coordinate the shipment of samples to the agreed upon collaborator or vendor.

5.9.2.4 Site(s) Performing Pharmacokinetics Testing
PK of NT-I7 will be performed by BioAgilytix.

5.9.3 *Cytokines, including IL-7*
Cytokine levels, including endogenous IL-7, will be evaluated before the first dose of NT-I7, and then again on time points described in Table 3.

5.9.3.1 Collection of Specimen(s)
Blood draws will be performed by venipuncture on study subjects. The collection will take place before NT-I7 injection when scheduled on the same day as NT-I7 administration.

5.9.3.2 Handling of Specimen(s)
Blood collection tubes (for subsequent PBMC and plasma isolation) will be shipped on day of blood draw for overnight delivery to the CIML.

5.9.3.3 Shipping of Specimen(s)
Blood collection tubes will be shipped overnight at ambient temperature to the CIML using CIML established SOPs. Clinical sites will utilize a web-based specimen system (BSI-Engage) to communicate with the CIML. The CIML will coordinate shipments of serum to the Fred Hutch Shared Resources lab, or vendor, as needed.

5.9.3.4 *Site(s) Performing Pharmacodynamic Testing*
Cytokine assays will be performed at the Fred Hutch Shared Resources or by agreed

upon vendor.

6. TREATMENT PLAN

Based on the pharmacodynamic data obtained from the GX-I7-CA-003 study (Q3W) dosing and preliminary data from other ongoing studies with less frequent dosing schedules, NT-I7 can be given less frequently than every three weeks and more frequently than every twelve weeks (e.g., Q9W), and will still lead to similar changes in the ALC and other peripheral blood T-cell subsets.

This is a Phase I, open-label, multicenter study to determine the safety and efficacy of NT-I7 in HIV-negative and HIV-positive patients with KS. A traditional 3+3 design (Figure 6) will be used, with DLT window being the first 28 days of study treatment. Three dose levels of NT-I7 will be administered, 480 µg/kg, 960 µg/kg and 1200 µg/kg injected on Day 1 ± 2 days of every cycle (every 9 weeks).

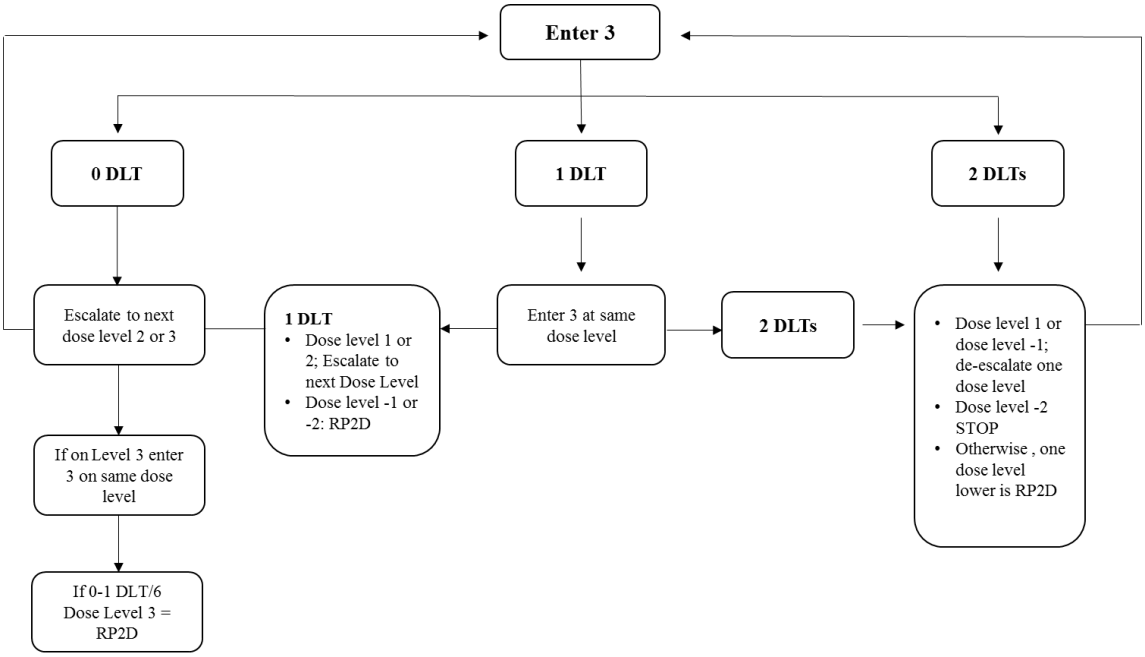


Figure 6: 3+3 Phase 1 study design schema.

All participants enrolled into this study will receive NT-I7 IM injections at the scheduled dose level (Table 8). Participants will be treated at a given dose level every 9 weeks for up to 27 weeks (4 doses) and followed for an additional 12 months. NT-I7 will be held if the ALC is greater than 10,000 cells/µL at the time of administration. There will be no intra-participant dose escalation.

Three participants will be enrolled at dose level 1. If 0 of 3 have a DLT (described in Section 6.2), dosing will escalate to the next dose level. If 1 of 3 have a DLT, that dose level will expand

to 6 participants. If 1 of 6 participants has a DLT, dosing will escalate to the next highest level. If 0-1 participant has a DLT at dose level 3, an additional 3 participants will be treated at that level.

If two participants have a DLT at dose level 1 or dose level -1, dosing will de-escalate to the next lowest level. Dose levels -1 (360 µg/kg) and -2 (240 µg/kg) have been defined if there is unexpected toxicity at dose level 1.

The recommended phase 2 dose (RP2D) will be selected according to the following logic, taking into account the MTD determination from the Dose Escalation Phase (Phase I) and the Maximum Effective Dose (MED) level which is defined as the dose level at which maximum effects on peripheral blood T-cell levels and intratumor T-cell levels are observed. The intratumor T-cell levels will dominate if the peripheral blood and intratumor T-cell levels differ. The available data will be assessed by the Protocol PI(s), the Protocol Chair, and the CITN Central Operating and Statistical Center (COSC) to select the RP2D.

- If the MTD is determined AND
  - MTD = MED, then the RP2D = MTD = MED
  - MTD > MED, then the RP2D = MED
- If the MTD is not reached, then the RP2D = MED

Treatment emergent adverse events will be tabulated according to grade and attribution (≥ possibly attributed to NT-I7 versus ≤ unlikely related to NT-I7).

Response to therapy will be evaluated by clinical exam using AIDS Clinical Trials Group Criteria ACTG criteria at baseline, 9 weeks, 13 weeks, 18 weeks, 27 weeks, and 36 weeks as outlined in the Trial Schema.

Table 8. NT-I7 Dose Escalation and De-Escalation Scheme.

Dose Level	NT-I7 Intramuscular (IM)	Route of Administration
DOSE LEVEL minus 2:	240 µg/kg	IM
DOSE LEVEL minus 1:	360 µg/kg	IM
DOSE LEVEL 1:	480 µg/kg	IM
DOSE LEVEL 2:	960 µg/kg	IM
DOSE LEVEL 3:	1200 µg/kg	IM

Abbreviation: IM=intramuscular

6.1 Agent Administration

Treatment will be administered on an outpatient basis. Reported adverse events and potential risks are described in Section 10. Appropriate dose modifications are described in Table 8 and Section 7. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

6.1.1 NT-I7

Subjects will receive NT-I7 IM injections on day 1 (± 2 days) of each cycle according to the dose escalation schedule described in Table 8. For information on the injection sites, please refer to Appendix B.

An adjusted body weight will be used to calculate the dose of NT-I7 for patients with a Body Mass Index (BMI) ›30 kg/m^2. Please refer to Appendix B for details on the adjusted body weight calculation. Weight must be collected at baseline and re-assessed prior to each NT-I7 dosing. If the patient's weight has changed ± 10% from the baseline measurement collected during screening, NT-I7 dose should be re-calculated based on the new weight.

Patients receiving NT-I7 will have their vital signs (heart rate, respiratory rate, blood pressure, and temperature) assessed within 60 minutes before the receiving the NT-I7 injection and will remain under observation for 4 hours after the first injection of NT-I7. Vital signs will be monitored every 2 hours during the post-injection observation period. Patients must be observed in clinic for at least 2 hours following subsequent administration of NT-I7 (Cycles 2, 3 and 4).

Patients will be informed about the possibility of the development of an allergic reaction to NT-I7 (hives, bronchospasm, rash, etc.) and instructed to contact their study physician if they develop such symptoms.

Table 9: Study Treatment Details

Regimen Description					
Agent	**Premedications; Precautions**	**Dose**	**Route**	**Schedule**	**Cycle**
rhIL-7-hyFc (NT-I7)	antihistamines or antipyretics/analgesics can be given prior to NT-I7 dosing[a]	Dose in µg/kg[b]	IM	Day 1 of each cycle	63 days

Abbreviations: IM=intramuscular.
[a]Not permitted for the first dose. Optional for subsequent injections.
[b]Refer to Table 8 for assigned dose level.

6.1.2 Other Procedures: Biopsy (core needle, punch or excisional)

Biopsy/tumor tissue will be obtained by punch biopsy, incisional or excisional biopsy. Core needle biopsy or excisional biopsy may be acceptable for visceral lesions depending on clinical circumstance.

Note: Baseline tumor biopsy (fresh) may be obtained up to 28 days prior to treatment initiation.

An archival tumor sample obtained within 1 year of screening is allowed if the pre-treatment biopsy is deemed unsafe or technically not feasible.

Tissue based studies will be performed on mandatory biopsies collected at baseline and at 9 weeks, with an optional biopsy at 13 weeks. Biopsy scheduled for collection at 9 weeks will be obtained prior to dosing on Cycle 2, Week 9, Day 1 or at the End of Treatment visit, whichever occurs first. Effect on tumor microenvironment will be assessed by multi-spectral IHC on serial biopsies.

6.2 Definition of Dose-Limiting Toxicity

Dose-limiting toxicity is defined as any AE occurring within the first 28 days (i.e., Cycle 1, Day 1 through Week 4 Day 7) that is considered to be at least possibly, probably, or definitely related to the protocol treatment (NT-I7) per the investigator, and that meets at least one of the non-hematologic or hematologic criteria below.

All toxicities will be graded using NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 or current version.

6.2.1 DLT Criteria

1. Grade ≥3 non-hematologic AE (not laboratory), with following exceptions:
    a. Grade ≥ 3 diarrhea, nausea, or vomiting that resolves within 2 days with use of anti-emetics or antidiarrheals per standard of care.
    b. Grade 3 fatigue lasting ≤ 3 days.
2. Grade 4 neutropenia lasting ≥ 5 days.
3. Febrile neutropenia Grade 3 or Grade 4:
    - Grade 3 is defined as absolute neutrophil count (ANC) < 1000/mm^3 with a single temperature of > 38.3 degrees C (101 degrees F) or a sustained temperature of ≥38 degrees C (100.4 degrees F) for more than 1 hour.
    - Grade 4 is defined as ANC < 1000/mm^3 with a single temperature of > 38.3 degrees C (101 degrees F) or a sustained temperature of ≥ 38 degrees C (100.4 degrees F) for more than 1 hour, with life-threatening consequences and urgent intervention indicated.
4. Other Grade 4 hematologic toxicity lasting ≥7 days, except thrombocytopenia:
    - Grade 4 thrombocytopenia of any duration.
    - Grade 3 thrombocytopenia associated with clinically significant bleeding.

    ***Note**:* Peripheral lymphocytopenia after the first NT-I7 injection is not a sign of toxicity; it reflects the lymphocytes "homing effect" of NT-I7. Lymphocyte counts usually come back to baseline 5 to 7 days after the first injection.
5. Any Grade 3 or Grade 4 non-hematologic laboratory value if:
    - Clinically significant medical intervention is required to treat the subject, or
    - AIDS defining opportunistic infection that occurs in the setting of new persistent

elevation of HIV viral load >400 copies/mL over 90 days despite adherence to ARV
- The abnormality leads to hospitalization.

6. Other Grade ≥ 3 clinical laboratory abnormalities must be reversible to ≤ Grade 1 within 72 hours with outpatient care and/or monitoring AND must not be considered clinically significant by the treating physician to be excluded from the definition of DLT.
7. Any treatment-related toxicity that causes the subject to discontinue treatment during Cycle 1.
8. Grade 5 toxicity.

Once all subjects in a cohort have completed the 4-week (28 days) DLT window, the AEs will be assessed by the Protocol PI(s), the Protocol Chair, and the CITN Central Operating and Statistical Center (COSC).

The subjects must complete the full 4-week DLT window to be considered evaluable for DLTs. Subjects who discontinue from the study before completion of the full 4-week DLT window for reasons other than the occurrence of a DLT (e.g., withdrawal of consent, rapid tumor progression, death due to rapid tumor progression, AE that does not meet DLT criteria) will not be considered evaluable for DLTs and will be replaced.

All subjects will be monitored for occurrence of DLT. Monitoring of all safety and toxicity data is done by the protocol PI and CITN COSC on a real-time basis as data are entered into Medidata Rave using the Web Reporting Module. All participating sites must notify the protocol PI and CITN COSC when a DLT has occurred.

6.3 General Concomitant Medication and Supportive Care Guidelines

Because there is a potential for interaction of NT-I7 with other concomitantly administered drugs, the case report form must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies. The PI should be alerted if the patient is taking any agent known to affect or with the potential for drug interactions. The study team should check a frequently-updated medical reference for a list of drugs to avoid or minimize use of.

6.3.1 General Concomitant Medication and Supportive Care Guidelines

Concomitant therapy includes any prescription medications or over-the-counter preparations used by a patient between the 7 days preceding the baseline evaluation and up to 30 days after the last dose of study treatment. Concomitant medications administered 30 days after the last dose of study treatment should be recorded for SAEs and events of special interest or clinical interest (ECIs) as defined in Section 10.

Subjects may receive medications that the investigator deems to be medically necessary, with the specific exception of non-protocol specified chemotherapy, radiotherapy, anti-neoplastic biological therapy or other investigational agents. Subjects who require the use of any of the aforementioned treatments for clinical management should be removed from the study during

that period. Standard antibiotic therapy will always be allowed.

Patients who experience hypersensitivity, potential allergic reaction or skin reaction, including injection-associated symptoms, may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or cimetidine or another H2 receptor antagonist, as per standard practice. Serious injection-associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with systemic corticosteroids, bronchodilators, intravenous fluid, epinephrine, or other supportive therapies as clinically indicated.

Topical corticosteroids to treat injection site reactions are allowed.

6.3.2 Excluded Therapies

If there is a clinical indication for using any medication or vaccination specifically prohibited during the study, discontinuation from study treatment or vaccination may be required. The final decision on any supportive therapy or vaccination rests with the investigator and/or the subject's primary physician. However, the decision to continue the subject on study treatment requires the mutual agreement of the investigator, the study sponsor and the subject. This includes but is not limited to the following therapies:

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in the protocol
- Investigational agents other than NT-I7
- Radiation therapy

  ***Note**:* Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed at the investigator's discretion.

- Live vaccines within 30 days prior to the first dose of study treatment and while participating in the study. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g., FluMist®) are live attenuated vaccines and are not allowed. Jynneos Monkeypox Vaccine is not considered a live virus vaccine in terms of eligibility or administration of NT-I7. Even though the Jynneos Monkeypox Vaccine can be considered a live virus because it does infect the cells upon injection, it is 'replication incompetent', so the localized infection caused by the vaccine cannot spread, and therefore poses a very low risk of complications associated viremia.

  - In participants who have not yet started treatment, Jynneos Monkeypox Vaccine should be administered at least 3 days prior to start of treatment when possible.
  - In participants who are receiving study therapy, Jynneos Monkeypox Vaccine should not be administered on the same day as IM injection of NT-I7. Where possible, the vaccine should be administered during an off week, or at least a week apart from an injection day. A minimum gap of at least 3 days is strongly recommended, based on CDC guidance that most vaccine-related adverse events occur within 3 days of injection.
  - Administration of Jynneos Monkeypox Vaccine should be documented as a concomitant medication.

- Systemic glucocorticoids for any purpose other than to modulate symptoms from an AE that is suspected to have an immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.

  ***Note**:* Inhaled steroids are allowed for management of asthma.
  ***Note**:* As stated in Section 6.3.1, topical corticosteroids to treat injection site reaction are allowed.

  - Immunostimulatory and immunosuppressive agents are prohibited.
  - No data exist regarding the interaction of NT-I7 with commonly used herbal or non-traditional medications. Patients should be instructed not to use such medications while receiving NT-I7 therapy or use with caution at the investigator's discretion. Close monitoring is required while the patient receives study treatment. Herbal therapy intended as anticancer therapy must be discontinued ≥ 1 week before initiation of study treatment.

6.3.3 Medications Used with Caution

No data exist regarding the interaction of NT-I7 with drugs known to prolong the QT/QTc interval. Accordingly, subjects receiving these drugs while receiving NT-I7 therapy should be closely monitored.

6.4 Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment may continue for *up to 27 weeks (4 cycles/doses)* or until one of the following criteria for discontinuation of therapy applies:

- Disease progression requiring systemic therapy
- Intercurrent illness that prevents further administration of treatment

- Unacceptable adverse event(s)
- Dose limiting toxicity
- Participant decides to withdraw from the study
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator
- Participant not adhering to study schedule and procedures
- Dosing interruption lasting >12 weeks
- Pregnancy
    - All women of child bearing potential should be instructed to contact the investigator immediately if they suspect they might be pregnant (*e.g.*, missed or late menstrual period) at any time during study participation.
    - The investigator must immediately notify CITN in the event of a confirmed pregnancy in a patient participating in the study.

- Termination of the study by sponsor
- The drug manufacturer can no longer provide the study agent

The reason(s) for protocol therapy discontinuation, the reason(s) for study removal, and the corresponding dates must be documented in the Case Report Form (CRF).

6.5 Study Treatment Beyond Progression

Immunotherapeutic agents such as NT-I7 may produce antitumor effects by potentiating endogenous cancer-specific immune responses. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents and can manifest as a clinical response after an initial increase in tumor burden or even the appearance of new lesions.

Patients may be treated beyond progression as measured by ACTG criteria up to 4 doses if they meet all of the following criteria:

- There is no indication for chemotherapy
- The PI suspects increases in lesion measurements may be due to pseudoprogression based on assessment of changes in tumor burden and tumor associated symptoms
- The patient is tolerating therapy without DLTs

- There is no decrement in performance status
- There is absence of symptoms and signs indicating clinically significant progression of disease
- There is absence of symptomatic rapid disease progression requiring urgent medical care

These criteria must be met to ensure that patients are not exposed to unreasonable risks by continued use of the investigation agent in spite of progression of disease.

Subjects should remain on the trial and continue to receive monitoring according to the Study Calendar (Section 11). In addition to routine monitoring, participants with KS progression will be evaluated in 4 weeks (±1 week) for follow-up tumor assessment and possible removal from study.

At the time of progression of disease, patients will be re-consented and adequately informed of all FDA-approved therapy and potential clinical benefit that the patient may be foregoing in order to continue receiving the investigational product.

6.6 Duration of Follow-Up

The active study will end when the last participant reaches 2 years.

Participants will be followed every 12 weeks for 12 months after the final dose of NT-I7, regardless of number of doses, to evaluate durability of T cell and tumor response. Participants will be taken off study after completing the 12 months of follow-up after final dose of NT-I7, or at investigator discretion or participant preference.

End of treatment visit should be performed 7 days after the last administration of either agent or immediately before initiation of any other cancer therapy.

After disease progression or start of new anticancer treatment, subject will be followed for survival every 12 weeks (± 1 week) until death, lost to follow-up, withdrawal of consent or the end of the study, whichever occurs first. Survival follow-up can be done either by in-person visit or by telephone assessment.

Subjects removed from study for unacceptable AE(s) will be followed until resolution or stabilization of the AE; in addition, the subjects will be followed for disease status and overall survival, as described above.

6.7 Patients Lost to Follow-Up

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

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

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.
- Before a subject is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.
- Should the subject continue to be unreachable, he/she will be considered to have withdrawn from the study.

7. DOSING DELAYS/DOSE MODIFICATIONS

The NCI CTCAE Version 5.0 will be used to grade AEs. Subjects enrolled in this study will be evaluated clinically and with standard laboratory tests before and at regular intervals during their participation in this study as specified in this section.

Subjects will be evaluated for treatment-emergent adverse events (all grades), SAEs and AEs requiring study drug interruption or discontinuation at each study visit for the duration of their participation in the study.

Clinical experience has demonstrated that development of autoimmune inflammatory conditions is a general risk with therapeutics intended to enhance anti-tumor T-cell responses. Such immune related AEs (irAEs) have been described for virtually all organ systems and include, but are not limited to, colitis, hepatitis, pneumonitis, endocrinopathy, ocular toxicity, pancreatic toxicity and rash.

The risk of development of autoimmune inflammatory condition related to NT-I7 seems relatively low. In the previous clinical studies with rhIL-7 and in the studies with single-agent NT-I7, including the completed FIH study GX-I7-HV-001 in normal healthy individuals with NT-I7, no irAEs were reported. In the completed study GX-I7-CA-003 in patients with advanced solid tumors one AE suggestive of autoimmune disease was reported. In the ongoing study NIT110, immune-mediated hepatitis and immune-mediated nephritis were reported as adverse drug reactions in patients receiving NT-I7 in combination with pembrolizumab.

Immune-related toxicities associated or possibly associated with NT-I7 should be closely monitored and carefully managed according to standard medical practice (e.g., thyroid hormone replacement for autoimmune hypothyroidism). Additional tests, such as autoimmune serology or biopsies, should be used to determine a possible immunogenic etiology. Although most irAEs observed with immune modulatory agents have been mild and self-limiting, such events should be recognized early and treated promptly to avoid potential major complications (Di Giacomo, Biagioli, and Maio 2010). Discontinuation of NT-I7 may not have an immediate therapeutic effect, and there is no available antidote for NT-I7. The primary approach to mild irAEs (Grades

1−2) is supportive and symptomatic care. In severe cases, irAEs may be acutely managed with systemic corticosteroids, mycophenolate or TNF-α antagonists.

Due to the potential risk of NT-I7 to induce autoimmune conditions, patients with a history of clinically significant autoimmune disease will be excluded from this trial.

Dose modifications for Adverse Events:

Adverse Events from NT-I7 are expected to be mild and infrequent, as well as transient and Grade 2 or less (as noted in the AE list, Section 10). If a patient experiences a clinically significant and/or unacceptable toxicity, dosing should be interrupted, or the dose should be reduced per guidelines below and supportive therapy administered per standard clinical practice.

A maximum of two dose reductions will be allowed for an individual patient. If the second dose reduction is not tolerated, study treatment should be permanently discontinued, and the patient should be followed for safety per protocol guidelines.

NT-I7 administration will be held if the ALC is greater than 10,000 cells/μL. A blood draw will be performed prior to dosing on Day 1 of each cycle. Elevated ALC levels which have not resolved to ≤ Grade 1 and/or requiring more than a 72-hour delay in administration of NT-I7 must be discussed with the Study Sponsor. Grade 3 lymphocyte count increase (>20,000 cells/μL) is a normal physiologic response to the study treatment.
Below are dose management tables for the following AEs: fatigue, nausea, vomiting, diarrhea, neutropenia, thrombocytopenia, and hepatic damage.

Event Name	**Fatigue**
Grade of Event	**Management/Next Dose for NT-I7**
≤ Grade 1	No change in dosing schedule
Grade 2	No change in dosing schedule
Grade 3	Hold* until ≤ Grade 2
Grade 4	Off protocol therapy
*Patients requiring a delay of >72 hours should go off protocol therapy.	
Recommended management: physician discretion	

Event Name	**Nausea**
Grade of Event	**Management/Next Dose for NT-I7**
≤ Grade 1	No change in dosing schedule
Grade 2	No change in dosing schedule
Grade 3	Off protocol therapy if with adequate/maximal medical intervention symptoms persist
Grade 4	Off protocol therapy
Patients requiring a delay of >72 hours should go off protocol therapy.	
Recommended management: antiemetics	

Event Name	Vomiting
Grade of Event	**Management/Next Dose for NT-I7**
≤ Grade 1	No change in dosing schedule
Grade 2	No change in dosing schedule
Grade 3	Off protocol therapy if with adequate/maximal medical intervention symptoms persist
Grade 4	Off protocol therapy
Patients requiring a delay of >72 hours should go off protocol therapy.	
Recommended management: antiemetics	

Event Name	Diarrhea
Grade of Event	**Management/Next Dose for NT-I7**
≤ Grade 1	No change in dosing schedule
Grade 2	No change in dosing schedule
Grade 3	Off protocol therapy if with adequate/maximal medical intervention symptoms persist
Grade 4	Off protocol therapy
Patients requiring a delay of >72 hours should go off protocol therapy.	
Recommended management: physician discretion	

Event Name	Neutropenia
Grade of Event	**Management/Next Dose for NT-I7**
≤ Grade 1	No change in dosing schedule
Grade 2	No change in dosing schedule
Grade 3	Hold* until ≤ Grade 2
Grade 4	Off protocol therapy
*Patients requiring a delay of >72 hours should go off protocol therapy.	
Recommended management: treatment of infection as appropriate	

Event Name	Thrombocytopenia
Grade of Event	**Management/Next Dose for NT-I7**
≤ Grade 1	No change in dosing schedule
Grade 2	No change in dosing schedule
Grade 3	Off protocol therapy
Grade 4	Off protocol therapy
Patients requiring a delay of >72 hours should go off protocol therapy.	
Recommended management: platelet transfusion if indicated	

Event Name	Hepatic Damage
Grade of Event	**Management/Next Dose for NT-I7**
≤ Grade 1	No change in dosing schedule
Grade 2	No change in dosing schedule[1]
Grade 3	Off protocol therapy
Grade 4	Off protocol therapy
Patients requiring a delay of >72 hours should go off protocol therapy.	
Recommended management: physician discretion	

Event Name	HIV Viremia
Grade of Event	**Management/Next Dose for NT-I7**
HIV RNA > lower limit of detection and 400 copies /mL	No change in dosing schedule. Monitor HIV viral load 4 weeks later.
HIV RNA >400-1000 copies/mL	Repeat measurement in 4 weeks. Hold next cycle until plasma HIV RNA < 400 copies/mL. Evaluate adherence to medication.
HIV RNA >1000 copies/mL	Repeat measurement in 4 weeks. Hold next cycle until plasma HIV RNA < 400 copies/mL. If repeat > 1000 copies/mL, evaluation for HIV drug resistance
DLT (Section 6.2.1.)	Off protocol therapy
Patients requiring a delay of >72 hours should go off protocol therapy.	
Recommended management: physician discretion	

8. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational agents administered in this study can be found in Section 10.1.

8.1 CTEP IND Agent(s): N/A

8.2 Other Investigational Agent

8.2.1 *NT-I7 (rhIL-7-hyFc), NSC # 805638*

Other Names: GX-I7 by Genexine, Inc

Classification: Cytokine

M.W.: 104 KDa

Mode of Action: Multifunctional cytokine critical for T-cell development and homeostasis.

Description: NT-I7 has a molecular weight of 104 KDa and is composed of 400 amino acids with 155 amino acids for IL-7 and 30 for the IgD hinge, 8 for IgD the CH2 domain, and 207 for the IgG4 region. NT-I7 contains 11 disulfide bonds, 1 O-glycosylation and 3 N-glycosylation sites. NT-I7 protein is produced by inserting the gene expressing rhIL-7-hyFc into the eukaryotic expression vector pAD15 at the Multiple Cloning Site. The CHO cell line DG44 is used to produce NT-I7.

How Supplied: NT-I7 is supplied by NeoImmuneTech, Inc. Each single-use 1.0 mL vial contains 25 mg of NT-I7 at a concentration of 25 mg/mL, as a sterile, clear, colorless solution, pH approximately 5. In addition to the active ingredient NT-I7 (rhIL-7-hyFc), each vial contains sucrose, D-sorbitol, tri-sodium citrate dihydrate, citric acid monohydrate, and Polysorbate 80 as a stabilizer and buffer. These ingredients meet the specification criteria of the European pharmacopeia (Ph. EUR).

Preparation: The entire preparation process should be carried out in a sterile environment to prevent possible contamination. The dose volume of NT-I7 will be determined based on the assigned dose level and the subject's body weight. For more information, please refer to Appendix B.

The site pharmacy must verify the total dose which is based on the subject's body weight with the site clinical team prior to NT-I7 preparation.

Registered research nurses may prepare NT-I7 syringes for administration. In such cases, site pharmacy will verify the total dose, based on the subject's body weight, with the site clinical team, and will dispense the vial(s) with pharmacy labeling indicating pharmacist-calculated dose volume to be withdrawn into syringe. Prior to administering NT-I7, two research nurses will verify the dose volume calculation and the volume of NT-I7 in the prepared syringe.

The NT-I7 finished drug product should be a colorless, clear solution and should not contain any particulate matter that can be observed visually. There should not be any floating particulates under gross observation. DO NOT SHAKE vials before injection.

Storage: Vials that contain NT-I7 must be kept refrigerated at 2~8°C. **NT-I7 vials should never be frozen or shaken**. It is recommended that vials are protected from direct light until the time of use.

If a storage temperature excursion is identified, promptly return NT-I7 to 2~8°C and quarantine the supplies. Provide a detailed report of the excursion to citn@fredhutch.org for determination of suitability.

Stability: The site pharmacy should prepare the NT-I7 dose syringes in proximity to the time of dose administration. Vials should be removed from the refrigerator 1 to 2 hours before use to achieve room temperature prior to administration. Vial contents should never be frozen or shaken. The room-temperature stability of NT-I7 has been confirmed in a vial for up to 48 hours and in a disposable syringe for up to 24 hours.

Route and Method of Administration: The maximum volume that may be administered per intramuscular (IM) injection is 1 mL. Dose volumes greater than 1 mL are to be divided into multiple injections. Inject slowly (over 10-20 seconds) into Deltoid muscle or muscle of the thighs or buttocks, away from joints, nerves or bones. Rotate injection sites with each injection. For information on the injection sites, please refer to Appendix B.

Patient Care Implications: Advise study subjects to use effective contraception while receiving study treatment and for at least 3 months (90 days) for both male participants and female participants after the last dose of study treatment.

For patients with a Body Mass Index (BMI) ›30 kg/m^2, an adjusted body weight will be used to calculate the final dose to be administered. Please refer to Appendix B for details on the adjusted body weight calculation.

8.2.2 Agent Ordering and Agent Accountability

NT-I7 will be supplied by NeoImmuneTech Inc. to each participating site. Instructions for ordering the agent can be found in the Study Procedures Manual for the study.

8.2.2.1 Agent Inventory Records

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, dispensing and final disposition of all agents received from NeoImmuneTech Inc. using the NCI Drug Accountability Record Form.

8.2.3 Investigator Brochure Availability

The current version of the IB for the agent will be distributed to site investigators and research staff by the CITN Central Operating and Statistical Center (COSC). Questions about the most current version of the IB may be directed to the CITN COSC via email.

8.2.4 Useful Links and Contacts

- CTEP Forms, Templates, Documents: http://ctep.cancer.gov/forms/
- NCI CTEP Investigator Registration: RCRHelpDesk@nih.gov
- CTEP Identity and Access Management account: https://ctepcore.nci.nih.gov/iam/
- CTEP IAM account help: ctepreghelp@ctep.nci.nih.gov

9. STATISTICAL CONSIDERATIONS

9.1 Study Design/Endpoints

9.1.1 **Primary Endpoint**

9.1.1.1 Adverse Events and Dose Limiting Toxicity

Three participants will be enrolled at dose level 1. If 0 of 3 have a DLT, dosing will escalate to the next highest dose level. If 1 of 3 have a DLT, that dose level will expand to 6 participants. If 1 of 6 participants has a DLT, dosing will escalate to the next highest level. If 0-1 participants have a DLT at dose level 3, an additional 3 participants will be treated at that level.

If 2 participants have a DLT at dose level 1 or dose level -1, dosing will de-escalate to the next lowest level. If 2 participants have a DLT as dose level -2, the study will be stopped.

The RP2D will be no higher than the highest dose at which 0-1 of 6 participants has a DLT, or the level below a dose level with 2 DLTs. Additional RP2D considerations will be based on PD of ALC, CD4+ and CD8+ T cell responses, and the totality of the AE beyond the 28-day window.

DLTs will be defined as any AE that is considered to be at least possibly, probably, or definitely related to the protocol treatment (NT-I7), that occurs within the first 28 days of dose 1 of NT-I7 (i.e., from Week 0 Day 1 through Week 4 Day 7) and that meets at least one of the non-hematologic or hematologic criteria defined in the protocol.

9.1.1.2 Primary Objective

To determine the safety and adverse event profile of NT-I7 dosed at 480 μg/kg, 960 μg/kg, and 1200 μg/kg in patients with KS with or without infection with HIV, including estimation of the maximum tolerated dose (MTD) and/or the recommended Phase 2 dose (RP2D).

9.1.1.3 Primary Hypothesis

NT-I7 dosed at 480 μg/kg, 960 μg/kg and 1200 μg/kg is safe and tolerable in patients with KS with or without infection with HIV.

9.2 Sample Size/Accrual Rate

Two participants at minimum and a maximum of 6 participants at each dose level will be treated. Up to 2 participants who do not complete at least one year of follow up for reasons other than toxicity or disease progression may be replaced. Up to twenty patients will be enrolled in the study.

This protocol is designed to meet clinical needs of women and members of minority groups. The planned enrollment report (below) is based on US HIV demographics and previous studies.

PLANNED ENROLLMENT REPORT

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/ Alaska Native		1			**1**
Asian		1			**1**
Native Hawaiian or Other Pacific Islander		1			**1**
Black or African American	1	4	1	3	**9**
White	0	3	0	3	**6**
More Than One Race	0	1	0	1	**2**
Total	**1**	**11**	**1**	**7**	**20**

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9.3 Stratification Factors

Patients will not be stratified.

9.4 Analysis of Secondary Endpoints

9.4.1 Objective Response Rate (ORR) to NT-I7 in HIV-positive and HIV-negative adults with KS

To preliminarily evaluate the objective response rate of KS to NT-I7 across all dose levels, KS response will be assessed according to modified ACTG criteria. For primary analysis the best response obtained within 12 months of the first dose of NT-I7 will be used, in all participants administered across study doses. Subset analyses for participants by dose level, HIV status, baseline CD4 greater than or less than 200 cells/uL, and history of prior chemotherapy for any subset in which there are at least 6 participants. A more precise estimate of efficacy will occur in a RP2D expansion cohort where dosing will be uniform. An expansion cohort will be included in an amendment.

9.4.2 Duration of Response, Progression-free Survival, and Overall Survival of HIV-positive and HIV-negative adults with KS Treated with NT-I7

Statistical methods for censored time-to-event data will be used to estimate overall survival, progression-free survival and duration of response along with 95% CI bands. Kaplan Meier survival estimates will be constructed for each of these survival endpoints with 95% CIs, for up to 1 year following initiation of treatment in all participants. Overall survival will be defined as the time from administration of the first dose of NT-I7 until death or censoring, progression free survival will be defined as the time from administration of the first dose of NT-I7 until disease progression or death or censoring, and duration of response will be measured in subjects who obtain a partial response or better and defined as time from the best response within the first 36 weeks of therapy until disease progression or censoring. Subsequently, Cox proportional hazards regression will be used to estimate hazard ratios with 95% CIs for HIV-positive versus HIV-negative participants, adjusted for disease stage.

9.4.3 Kinetics of CD4+ and CD8+ T cells in blood, and on levels and phenotype within tumors, using flow cytometry and immunohistochemistry, respectively.

It is hypothesized that NT-I7 will lead to T cell expansion over the first 4-8 weeks after administration and that increases will be measurable in the blood using total blood counts with automated differentials and flow cytometry and in tumors by immunohistochemistry at 9 weeks. For blood measurements, ALC will be measured primarily, while absolute CD4+ and CD8+ T cell will be evaluated secondarily. Tumor infiltrating lymphocytes (TILs) will be evaluated quantitatively (cells/hpf) with qualitative annotation of the pattern of distribution.

For analysis of circulating lymphocytes we will first describe fold-change (median and range) in blood ALC from pre-administration to each time point following first administration (1, 4, and 9 weeks), and by category of selected participant characteristics (e.g., dose level, age [by decade], sex, HIV status, prior systemic therapy, and in HIV+, by CD4+ T cells ($<$ versus $\geq$ 200 cells/uL). More formally, we will explore multilevel negative binomial regression to estimate fold-change from pre-administration, adjusted for NT-I7 dose, HIV status, prior therapy, and baseline CD4+ T cell counts. In this analysis, ALC is the dependent variable and a generalized linear mixed model is applied with time from administration (weeks), an indicator of first or second administration, and gap between first and second administration as independent variables of interest in addition to adjustment variables. A random intercept is included for each participant to incorporate correlation between T cell counts from the same participant. The exponentiated fixed-effects model coefficients estimate fold-change from baseline with 95% CIs for a representative participant.

The same analytic approach will be applied to analysis of CD4+ and CD8+ T cells separately, and to TIL counts.

9.4.4 Immunogenicity of NT-I7 in participants with KS

The proportion of participants developing neutralizing antibodies will be summarized.

10. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of AEs (Section 10.1.2) and the characteristics of an observed AE (Sections 10.2 and 10.3) will determine whether the event requires expedited reporting via the CTEP Adverse Event Reporting System (CTEP-AERS) **in addition** to routine reporting.

10.1 Comprehensive Adverse Events and Potential Risks Lists(s) (CAEPRs): N/A

10.1.1 CAEPRs for CTEP IND Agent(s): N/A

10.1.2 Adverse Event List for NT-I7 (NSC 805638)

Data from two completed clinical studies and interim safety data from seven ongoing studies indicate that NT-I7 has been well tolerated with predominantly Grade 1 and Grade 2 AEs, two treatment-related Grade 4 AEs, and no Grade 5 AEs. Increases in ALC have been observed following treatment (after an initial decrease) with peak effect approximately three weeks after treatment.

10.1.2.1 Completed Study GX-I7-HV-001

A total of 58 treatment-emergent adverse events (TEAEs) were reported by 26 of 30 subjects (86.7%). In each NT-I7 treatment group, 8 of 8 subjects (100.0%) reported TEAEs compared with 2 of 6 subjects (33.3%) in the placebo group. The majority of TEAEs were mild in intensity. Most TEAEs were considered probably or possibly related to study drug. There were no serious TEAEs or TEAEs leading to death reported during the study.

All TEAEs had resolved by follow-up. The most frequent AEs were injection site reactions, headache, and productive cough. Injection site reactions were considered related to the study drug and were much milder after IM administration than after SQ administration. No other clinically significant abnormalities were found in clinical laboratory tests, vital signs, 12-lead electrocardiogram (ECG), or physical examinations. More details are provided in the NT-I7 Investigator's Brochure.

10.1.2.2 Completed Study GX-I7-CA-003

A total of 225 TEAEs occurred in 35 subjects (100.0%). By dose group, 14 TEAEs were reported in the NT-I7 60 µg/kg group, 30 TEAEs in the NT-I7 120 µg/kg group, 15 TEAEs in the NT-I7 240 µg/kg group, 21 TEAEs in the NT-I7 480 µg/kg group, 35 TEAEs in the NT-I7 720 µg/kg group, 6 TEAEs in the NT-I7 960 µg/kg group, 88 TEAEs in the NT-I7 1200 µg/kg group, and 16 TEAEs in the 1700 µg/kg group. When the severity of AEs was graded using the NCI-CTCAE (Version 4.0), 118 TEAEs were mild (Grade 1), 84 TEAEs were moderate (Grade 2), 16 TEAEs were severe (Grade 3), and 4 TEAEs were life-threatening or required urgent intervention (Grade 4). Three TEAEs were reported as death related to AEs (Grade 5). During the study, there were 3

subjects who experienced 4 SAEs that resulted in death. All deaths were considered not related to NT-I7.

By preferred term (PT), the most common AEs were injection site reactions (61 TEAEs in 25 subjects [71.4%]), pyrexia (26 TEAEs in 15 subjects [42.9%]), and abdominal pain (10 TEAEs in 10 subjects [28.6%]).

There were 6 SAEs in 5 subjects (14.29%): 1 subject in the 120 μg/kg group had Grade 5 mesenteric arterial occlusion (not related to NT-I7); 1 subject in the 480 μg/kg group had Grade 3 ascites and Grade 5 upper gastrointestinal hemorrhage (both not related); 2 subjects in the 1200 μg/kg group had Grade 2 azotemia and Grade 5 dyspnea (both not related); and 1 subject in the 1700 μg/kg group had Grade 3 hypersensitivity (related). The last event was also a serious ADR.

Adverse drug reactions were AEs that could not be completely excluded from relationship to study drug. A total of 116 ADRs occurred in 28 of 35 subjects (80.0%). All of the ADRs were determined to be related to study drug. By dose group, 3 subjects (100.0%, 6 events) reported ADRs in the NT-I7 60 μg/kg group, 2 subjects (66.7%, 9 events) reported ADRs in the NT-I7 120 μg/kg group, 3 subjects (100.0%, 6 events) reported ADRs in the NT-I7 240 μg/kg group, 2 subjects (66.7%, 8 events) in the NT-I7 480 μg/kg group, 4 subjects (66.7%, 18 events) reported ADRs in the NT-I7 720 μg/kg group, 2 subjects (66.7%, 4 events) reported ADRs in the NT-I7 960 μg/kg group, 10 subjects (83.3%, 49 events) reported ADRs in the NT-I7 1200 μg/kg group, and 2 subjects (100.0%, 16 events) reported ADRs in the NT-I7 1700 μg/kg group (Table 11).

When the severity of ADRs was graded using the NCI-CTCAE (Version 4.0), 68 cases were mild (Grade 1), 43 cases were moderate (Grade 2), 5 cases were severe (Grade 3), and no ADR was reported as Grades 4 or 5. The most frequently reported ADRs were: injection site reaction (25 subjects, 71.4%, 61 events); pyrexia (12 subjects, 34.3%, 21 events); rash or rash papular (8 subjects, 22.9%, 9 events); fatigue, influenza like illness, and urticaria (each 4 subjects, 11.4%, 4 events); asthenia, pruritis, and decreased appetite (each 2 subjects, 5.7%, 2 events); and erythema, anaphylactic reaction, hypersensitivity, back pain, myalgia, nausea, and platelet count decreased (each 1 subject, 2.9%, 1 event). More details are provided in the NT-I7 Investigator's Brochure.

There were 10 AEs of special interest (AESI) as specified in the protocol in 5 subjects. The AESI included cases of potential drug-induced liver injury, conditions suggestive of autoimmune disorders, Grade 2 or higher AEs suggestive of hypersensitivity or immune-mediated reaction, Grade 2 or higher hypoxia or dyspnea, and Grade 2 or higher pleural effusion. One AESI (pneumonia) occurred in 2 subjects, all others were reported for a single subject (anaphylactic reaction, hypersensitivity, mesenteric arterial occlusion, pyrexia, hepatic failure, pleural effusion, urticaria, and hypotension).

One of 2 subjects at 1700 μg/kg experienced DLT (hypersensitivity) as specified in the protocol. The RP2D and MTD of NT-I7 was determined to be 1200 μg/kg.

Clinically significant changes in plasma and serum chemistry results after the administration of study drug were reported as AEs or were judged to be due to progression of the underlying disease.

The assessment of localized resistance of the injection site was made through patient interviews or observation of the injection site at each visit. The result of a localized resistance assessment determined clinically significant by the investigator was collected as an injection site reaction (ISR). A total of 61 ISRs occurred in 25 of 35 subjects (71.4%). The severity of all ISR AEs was Grade 1 or Grade 2.

Clinically significant results of physical examination and results of localized resistance assessment after the administration of the study drug were all reported as AEs, and no clinically significant results related to the study drug were found in other safety assessments such as vital signs, ECGs, and laboratory tests.

10.1.2.3 Ongoing Study NIT-104/ABTC-103

A total of 261 TEAEs occurred in 12 of 12 (100%) total subjects. When the severity of AEs was graded using the NCI-CTCAE (Version 5.0), 151 TEAEs were mild (Grade 1), 74 TEAEs were moderate (Grade 2), 33 TEAEs were severe (Grade 3), and 3 TEAEs were life-threatening or required urgent intervention (Grade 4). There were 3 SAEs reported as seizure in 2 subjects (16.7%). One subject had 1 SAE of seizure that was considered unlikely related to NT-I7. A second subject had 2 SAEs of seizure that were both considered not related to NT-I7.

A total of 9 ADRs has occurred in 4 (3.3%) subjects. When the severity of ADRs was graded using the NCI-CTCAE (Version 5.0), 6 ADRs were mild (Grade 1), 2 ADRs were moderate (Grade 2), and 1 ADR was severe (Grade 3). No ADR was reported as Grade 4 or 5. The most common ADR was rash maculo-papular (28.6%). More details are provided in the NT-I7 Investigator's Brochure.

10.1.2.4 Ongoing Study NIT-106

A total of 375 TEAEs occurred in 24 of 27 (88.9%) subjects overall. By dose group, 54 TEAEs were reported in the NT-I7 120 µg/kg group, 31 TEAEs in the NT-I7 360 µg/kg group, 178 TEAEs in the 840 µg/kg group, and 49 TEAEs in the 1200 µg/kg group. When the severity of AEs was graded using the NCI-CTCAE (Version 5.0), 242 TEAEs were mild (Grade 1), 88 TEAEs were moderate (Grade 2), 40 TEAEs were severe (Grade 3), and 2 TEAEs were life-threatening or required urgent intervention (Grade 4). Three Grade 5 TEAEs resulted in death; one Grade 5 TEAE was due to disease progression, and two Grade 5 TEAEs were due to neoplasms benign, malignant and unspecified (including cysts and polyps).

There were 830 SAEs reported in 313 subjects. One SAE occurred in 1 subject in the NT-I7 120 µg/kg + atezolizumab 1200 mg dose group, and the remaining 720 SAEs occurred in 1 subject5 subjects in the NT-I7 840 µg/kg + atezolizumab 1200 mg dose group., 1 SAE occurred in 1 subject in the NT-I7 1200 µg/kg + atezolizumab 1200 mg dose group, and the remaining 8 SAEs occurred in 6 subjects in Arm II. The SAEs included 2 events of each of acute kidney injury, dehydration, sepsis, lymphocyte count decreased, and 1 event each of fatigue, AST increased, confusional state, immune-mediated hepatitis, urinary tract infection, nausea, vomiting, and an uncoded AE.

A total of 185 ADRs has occurred in 24 of 27 (88.9%) subjects. When the severity of ADRs was graded using the NCI-CTCAE (Version 5.0), 132 ADRs were mild (Grade 1), 42 ADRs were moderate (Grade 2), and 11 ADRs were severe (Grade 3). No ADR was reported as Grade 4 or 5. ADRs reported for 3 subjects were 34 events of an uncoded ADR, 23 events of injection site reaction, 10 events of fatigue, 6 events of pruritis, 4 events each of oedema peripheral, anemia, and nausea, and 3 events each of the following: influenza like illness, hypothyroidism, appetite, hyperhidrosis, headache, vomiting, and alanine aminotransferase increased. More details are provided in the NT-I7 Investigator's Brochure.

10.1.2.5 Ongoing Study NIT-109

A total of 18 TEAEs occurred in 5 of 6 (83.3%) total subjects When the severity of AEs was graded using the NCI-CTCAE (Version 5.0), 12 TEAEs were mild (Grade 1), 4 TEAEs were moderate (Grade 2), and 2 TEAEs were severe (Grade 3). No Grade 4 or 5 TEAEs were reported.

The 2 SAEs reported were hepatic failure and urinary tract bleeding in 2 subjects (33.3%).

A total of 49 ADRs occurred in 4 (66.7%) subjects. When the severity of ADRs was graded using the NCI-CTCAE (Version 5.0), 5 ADRs were mild (Grade 1), and 4 ADRs were moderate (Grade 2). No ADR was reported as Grade 3, 4, or 5. The most commonly reported ADR was rash erythematous. More details are provided in the NT-I7 Investigator's Brochure.

10.1.2.6 Ongoing Study NIT-110

A total of 1493 TEAEs occurred in 131 of 133 (98.5%) subjects. By dose group, in dose escalation phase, 65 TEAEs were reported in the NT-I7 480 µg/kg group, 34 TEAEs in the NT-I7 960 µg/kg group, and 112 TEAEs in the 1200 µg/kg group. By dose group, in dose expansion phase, 83 TEAEs were reported in Arm I, 350 TEAEs in Arm II, 31 TEAEs in Arm III, 402 TEAEs in Arm IV, and 365 TEAEs in Arm V. In the Biomarker Cohort (NT-I7 [960 µg/kg]), 51 TEAEs were reported.

When the severity of AEs was graded using the NCI-CTCAE (Version 5.0), in total 863 TEAEs were mild (Grade 1), 438 TEAEs were moderate (Grade 2), 175 TEAEs were severe (Grade 3), and 5 TEAEs were life-threatening or required urgent intervention (Grade 4). Ten Grade 5 TEAEs resulted in death. Two TEAEs with no grade were reported as missing.

A total of 119 SAEs were reported in 67 subjects (50.4%). The SAEs included 9 events of pneumonia, 8 events of abdominal pain, 6 events of hyponatraemia, 4 events each of acute kidney injury and dyspnoea, and 3 events each of cerebrovascular accident, disease progression, pneumonitis, and vomiting.

A total of 656 ADRs were reported in 100 of 133 (75.2%) subjects. When the severity of ADRs was graded using the NCI-CTCAE (Version 5.0), 403 ADRs were mild (Grade 1), 199 ADRs were moderate (Grade 2), 52 ADRs were severe (Grade 3), and 2 ADRs were life-threatening or

required urgent intervention (Grade 4). No ADR was reported as Grade 5. ADRs reported for >10 subject were 100 events of injection site reaction, 59 events of rash maculo-papular, 47 events of fatigue, 36 events each of pruritus and pyrexia, 28 events of nausea, 26 events of oedema peripheral, 22 events of urinary tract infection, 17 events each of chills and vomiting, 16 events of influenza like illness, 15 events of injection site pain, and 11 events of injection site erythema. More details are provided in the NT-I7 Investigator's Brochure.

10.1.2.7 Ongoing Study NIT-112

A total of 67 TEAEs occurred in 5 of 5 (100%) total subjects. When the severity of AEs was graded using the NCI-CTCAE (Version 5.0), 35 TEAEs were mild (Grade 1), 18 TEAEs were moderate (Grade 2), 11 TEAEs were severe (Grade 3), and 3 TEAEs were life-threatening or required urgent intervention (Grade 4). No Grade 5 TEAEs were reported.

No SAE was reported in this study as of 31 May 2022.
A total of 4 ADRs has occurred in 3 (60.0%) subjects. When the severity of ADRs was graded using the NCI-CTCAE (Version 5.0), 3 ADRs were mild (Grade 1) and 1 ADR was moderate (Grade 2). No ADR was reported as Grade 3, 4, or 5. The most commonly reported ADR was injection site reaction. More details are provided in the NT-I7 Investigator's Brochure.

10.1.2.8 Ongoing Study NIT-116

A total of 75 TEAEs have occurred in 7 of 7 (100%) total subjects. When the severity of AEs was graded using the NCI-CTCAE (Version 5.0), 55 TEAEs were mild (Grade 1), 13 TEAEs were moderate (Grade 2), and 7 TEAEs were severe (Grade 3). No Grade 4 or 5 TEAEs were reported.

There was only 1 SAE reported as COVID-19 pneumonia in 1 subject (14.3%).

A total of 33 ADRs have occurred in 4 (57.1%) subjects. When the severity of ADRs was graded using the NCI-CTCAE (Version 5.0), 24 ADRs were mild (Grade 1), 6 ADRs were moderate (Grade 2), and 3 ADRs were severe (Grade 3). No ADR was reported as Grade 4 or 5. ADRs reported for >1 subject were 5 events of injection site erythema and 3 events each of the following: fibrin D dimer increased, injection site pruritus, and injection site swelling.

10.1.2.9 Ongoing Study NIT-119

A total of 76 TEAEs occurred in 13 of 15 (86.7%) total subjects. When the severity of AEs was graded using the NCI-CTCAE (Version 5.0), 41 TEAEs were mild (Grade 1), 21 TEAEs were moderate (Grade 2), and 10 TEAEs were severe (Grade 3). No Grade 4 and four Grade 5 TEAEs were reported.

Eleven SAEs were reported in 7 subjects (46.7%). The most commonly occurring SAEs included 2 events each of death and disease progression.

A total of 42 ADRs have occurred in 11 (73.3%) subjects. When the severity of ADRs was

graded using the NCI-CTCAE (Version 5.0), 26 ADRs were mild (Grade 1), 11 ADRs were moderate (Grade 2), and 5 ADRs were severe (Grade 3). No ADR was reported as Grade 4 or 5. ADRs reported for >1 events in subjects were 6 events of rash maculo-papular, 4 events each of fatigue and injection site reaction, and 2 events each of the following: alanine aminotransferase increased, aspartate aminotransferase increased, constipation, and haematoma.

Note: NT-I7 in combination with other agents could cause an exacerbation of any AE currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

10.1.3 Adverse Event List(s) for Commercial Agent(s): N/A

10.2 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** 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 website http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

10.3 Expedited Adverse Event Reporting

10.3.1 Rave-CTEP-AERS Integration

The Rave Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS) Integration enables evaluation of Adverse Events (AE) entered in Rave to determine whether they require expedited reporting and facilitates entry in CTEP-AERS for those AEs requiring expedited reporting. **Sites must initiate all AEs for this study in Medidata Rave.**

Treatment-emergent AEs: All AEs that occur after start of treatment are collected in Medidata Rave using the Adverse Event form, which is available for entry at each treatment course or reporting period and is used to collect AEs that start during the period or persist from the previous reporting period. Adverse Events that occur 30 Days after the Last Administration of the Investigation Agent/Intervention are collected using the Late Adverse Event form. the.

Prior to sending AEs through the rules evaluation process, site staff should verify the following on the Adverse Event form in Rave:

- The reporting period (course/cycle) is correct, and
- AEs are recorded and complete (no missing fields) and the form is query-free.

The CRA reports AEs in Rave at the time the Investigator learns of the event. If the CRA modifies an AE, it must be re-submitted for rules evaluation.

Upon completion of AE entry in Medidata Rave, the CRA submits the AE for rules evaluation by completing the Expedited Reporting Evaluation form. Both NCI and protocol-specific reporting rules evaluate the AEs submitted for expedited reporting. A report is initiated in CTEP-AERS using information entered in Medidata Rave for AEs that meet reporting requirements. The CRA completes the report by accessing CTEP-AERS via a direct link on the Medidata Rave Expedited Reporting Evaluation form. Contact the CTSU Help Desk at 1-888-823-5923 or by email at ctsucontact@westat.com if you have any issues submitting an expedited report in CTEP-AERS.

In the rare occurrence that Internet connectivity is lost, a 24-hour notification is to be made to CITN by telephone at 206-667-2541. Once Internet connectivity is restored, the 24-hour notification that was phoned in must be entered immediately into CTEP-AERS using the deep link from Medidata Rave.

Additional information about the CTEP-AERS integration is available on the CTSU members' website:

- Study specific documents: Protocols > Documents > *Protocol Related Documents* >*Adverse Event* Reporting; and :
- Additional resources > *CTSU Operations Information* > User Guides & Help Topics.

NCI requirements for SAE reporting are available on the CTEP website:

- NCI Guidelines for Investigators: Adverse Event Reporting Requirements is available at https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf.

10.3.2 Distribution of Adverse Event Reports

CTEP-AERS is programmed for automatic electronic distribution of reports to the following individuals: Principal Investigator and Adverse Event Coordinator(s) (if applicable) of the Corresponding Organization or Lead Organization, the local treating physician, and the Reporter and Submitter. CTEP-AERS provides a copy feature for other e-mail recipients.

10.3.3 Expedited Reporting Guidelines

Use the NCI protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

Note: A death on study requires <u>both</u> routine and expedited reporting, regardless of causality as long as the death occurred within 30 days after the last administration of the investigational agent. Attribution to treatment or other cause must be provided.

Death due to progressive disease should be reported as **Grade 5 "Disease progression"** in the system organ class (SOC) "General disorders and administration site conditions." Evidence that the death was a manifestation of underlying disease (*e.g.*, radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

Phase 1 and Early Phase 2 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention [1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **<u>MUST</u>** immediately report to the sponsor **<u>ANY</u>** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)
An adverse event is considered serious if it results in **<u>ANY</u>** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon 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. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

<u>ALL</u> <u>SERIOUS</u> adverse events that meet the above criteria MUST be immediately reported to the NCI via electronic submission within the timeframes detailed in the table below.

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3-5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days	24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required	

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR.

<u>Expedited AE reporting timelines are defined as:</u>

- "24-Hour; 5 Calendar Days" - The AE must initially be submitted electronically within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted electronically within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:
Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 3, 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

[2]For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: May 5, 2011

10.3.4 Additional Protocol-Specific Expedited Adverse Event Reporting Exclusions: N/A

10.4 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions. **AEs reported expeditiously through CTEP-AERS must <u>also</u> be reported in routine study data submissions.**

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. AEs are reported in a routine manner at scheduled times during the trial using Medidata Rave. For this trial the Adverse Event CRF is used for routine AE reporting in Rave.

10.5 Pregnancy

Although not an adverse event in and of itself, pregnancy as well as its outcome must be documented via **the EDC**. Any pregnancy occurring in a patient or patient's partner from the time of consent to 90 days after the last dose of study drug must be reported to the CITN COSC and then followed for outcome. Newborn infants should be followed until 30 days old.

10.6 Secondary Malignancy

A *secondary malignancy* is a cancer caused by treatment for a previous malignancy (*e.g.*, treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

CTEP requires all secondary malignancies that occur following treatment with an agent under an NCI IND/IDE be reported expeditiously via CTEP-AERS. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (*e.g.*, acute myelocytic leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

10.7 Second Malignancy

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

11. STUDY CALENDAR

Clinical and laboratory evaluations are to be conducted within 2 weeks prior to start of protocol therapy. Scans and x-rays must be done ≤4 weeks prior to the start of therapy. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy.

Trial Period	**Screening Visit**	**Treatment Cycles[a]**							**End of Treatment[b]**	**Post-Treatment Follow-up**		
	D-28 to D-1	Cycle 1			Cycle 2		Cycle 3	Cycle 4		Other Off Treatment/ Safety FU[c]	Disease Assessment[d]	Survival FU[d]
Treatment Week:		0	1	4	9	13	18	27	36[b]			
Scheduling Window (Days):			±2	±2	±2	±2	±2	±2	At time of D/C ±7 days	30 ± 7 days post D/C	Every 12 weeks ± 7 days	Every 12 weeks ± 7 days
NT-I7[e,v]		X			X		X	X				
Administrative Procedures												
Informed Consent[f]	X											
Demographics and Medical History	X											
Prior and Concomitant Medication[g]	X ----------X									X		
Inclusion/Exclusion Criteria	X											
Clinical Procedures/Assessments[h]												
Physical Examination	X				X		X	X	X	X	X	
Vital Signs, Height, and Body Weight[i]	X	X			X		X	X	X	X	X	
Electrocardiogram[h]	X											
Chest X-Ray	X											
ECOG Performance Status	X	X			X		X	X	X	X	X	
Adverse Event Evaluation[j]		X----------X										
Laboratory Procedures/Assessments[k]												
CBC with Differential	X	X	X	X	X	X	X	X	X	X		
Comprehensive Serum Chemistry Panel[l]	X	X	X	X	X	X	X	X	X	X		
HIV Viral Load[m]	X	X		X	X	X	X	X	X	X		
T3, FT4 and TSH	X	X		X	X		X	X	X	X		
Urinalysis	X	X		X	X		X	X	X			
Pregnancy Test – Urine or Serum HCG[n]	X	X			X		X	X	X			

Trial Period	**Screening Visit**	**Treatment Cycles[a]**							**End of Treatment[b]**	**Post-Treatment Follow-up**		
	D-28 to D-1	Cycle 1			Cycle 2		Cycle 3	Cycle 4		Other Off Treatment/ Safety FU[c]	Disease Assessment[d]	Survival FU[d]
Treatment Week:		0	1	4	9	13	18	27	36[b]			
Scheduling Window (Days):			±2	±2	±2	±2	±2	±2	At time of D/C ±7 days	30 ± 7 days post D/C	Every 12 weeks ± 7 days	Every 12 weeks ± 7 days
Efficacy Measurements[o]												
KS Measurements/Response Evaluation	X	X			X	X	X	X	X		X	
Tumor Biopsies/Archival Tissue Collection[p]												
Biopsy Specimen Collection		X[q]			X[r]	X[s]			X[r]			
Correlative Studies Blood[t]												
T cell (CD4+ and CD8+) count		X	X	X	X	X	X					
Immunogenicity: ADA and NADA		X			X		X	X	X			
Immunophenotyping		X[u]	X[u]	X[u]	X[u]	X[u]	X[u]					
KSHV Humoral Responses		X[u]		X[u]	X[u]				X[u]			
KSHV PBMC Viral Load		X		X	X				X			
Anti-KSHV Immune T-cell Response		X[u]			X[u]				X[u]			
TCR Clonality		X		X	X		X	X				
IL-7		X		X	X		X	X				
NT-I7 PK[w]		X[w]	X		X[w]		X[w]	X[w]	X			

a. Treatment cycle: A given dose level of NT-I7 will be administered on Day 1 (±2 days) of each 9-week cycle (4 doses).
b. End of treatment (EOT) visit should be performed on week 36 (± 7days), or ≤ 7 days after the last dose of IP, or immediately before initiation of a new anticancer therapy for participants who require therapy before week 36, whichever is sooner.
c. Follow-up visit should be performed 30 days (±7 days) after the last dose of IP, and before subsequent therapy for participants who come off treatment before week 36 due to progressive disease, as well as for those who come off treatment before week 36 for reasons other than progression.
d. Disease assessment per standard of care every 12 weeks (±7 days) for 12 months. Study participants who start new anticancer treatment or discontinue study treatment due to documented disease progression will be followed for survival only every 12 weeks (±1 week) until death, lost to follow-up, withdrawal of consent or the end of the study, whichever occurs first. Survival follow-up can be done either by in-person visit or by telephone assessment.
e. Three dose levels of NT-I7 will be administered, 480 µg/kg, 960 µg/kg and 1200 µg/kg injected on the first day (± 2 days) of every cycle.
f. Written informed consent and any locally required privacy act document authorization must be obtained prior to performing any protocol-specific procedures, including screening evaluations. The written informed consent includes genetic sample collection and analysis. Informed consent and other administrative procedures must be performed within 28 days of treatment initiation.
g. Concomitant therapy includes any prescription medications or over-the-counter preparations used by a patient between the 7 days preceding the baseline evaluation and up to 30 days after the last dose of study treatment. Concomitant medications administered 30 days after the last dose of study treatment should be recorded for SAEs as defined in Section 10.
h. Whenever electrocardiograms (ECGs), vital signs, and blood draws are scheduled for the same time, the assessments should occur in the following order: ECG, vital signs, blood draws.
i. Height will be measured at screening only. Body weight will be measured at every visit. Vital signs (heart rate, respiratory rate, blood pressure, and temperature) will be assessed within 60 minutes before receiving the NT-I7 injection.

j. Treatment-emergent adverse events (TEAEs) will be collected and recorded in the eCRFs from the time of the first NT-I7 injection until 30 days after the last dose of IP. Dose-limiting toxicity (DLT) is defined as any AE that is considered to be at least possibly, probably, or definitely related to the protocol treatment (NT-I7), that occurs within the first 28 days of dose 1 of NT-I7 (i.e., from Week 0 Day 1 through Week 4 Day 7) and that meets at least one of the non-hematologic or hematologic criteria defined in the protocol.
k. Clinical laboratory safety tests do not need to be repeated on Cycle 1, Day 1 if the screening laboratory assessments are performed within 7 days prior to Cycle 1, Day 1. Serum or plasma clinical chemistry (including liver function test [LFT] monitoring) and hematology may be performed more frequently if clinically indicated. After Cycle 1, laboratory tests can be done up to 72 hours prior to the scheduled timepoint/treatment.
l. Comprehensive Metabolic Panel should include the following: glucose, calcium, sodium, potassium, carbon dioxide, chloride, albumin, total protein, alkaline phosphatase (ALP), alanine transaminase (ALT), aspartate aminotransferase (AST), total bilirubin, blood urea nitrogen (BUN), and creatinine.
m. Patients with confirmed HIV diagnosis prior to enrollment will have HIV Viral Load samples collected during screening, at baseline, while on study treatment, and at the End of Treatment visit.
n. Female patients of childbearing potential must have a negative urine or serum pregnancy test within 72 hours before receiving the study agent. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
o. Response to therapy will be evaluated by clinical exam using AIDS Clinical Trials Group Criteria ACTG criteria at baseline, 9 weeks, 13 weeks, 18 weeks, 27 weeks, and 36 weeks. If a participant has an abnormal chest X-ray on screening, chest x-ray or other imaging should be followed during response evaluation. In addition to routine monitoring, participants with KS progression will be evaluated in 4 weeks (±1 week) for follow-up tumor assessment and possible removal from study.
p. Tumor tissue will be obtained generally by punch biopsy, incisional or excisional biopsy. Core needle biopsy or excisional biopsy may be acceptable for visceral lesions depending on clinical circumstance. Tissue based studies will be performed on mandatory biopsies collected at baseline and at 9 weeks, with an optional biopsy at 13 weeks (4 weeks after dose 2).
q. Baseline tumor biopsy (fresh) must be obtained within 28 days of treatment initiation. An archival tumor sample obtained within 1 year of screening is allowed if the pre-treatment biopsy is deemed unsafe or technically not feasible.
r. Post-treatment tumor biopsy will be obtained prior to dosing on Cycle 2, Week 9, Day 1 or at the End of Treatment visit, whichever occurs first.
s. Tissue biopsy at 13 weeks is *optional*.
t. Correlative studies blood draws must be performed prior to NT-I7 injection when scheduled on the same day as NT-I7 administration. See Section 5 for details of correlative studies.
u. This correlative studies blood draw is *optional*.
v. NT-I7 will be held if the ALC is greater than 10,000 cells/µL at the time of administration.
w. Two PK blood draws for the indicated timepoints should be performed as follows: 1) a 7 ml draw prior to NT-I7 administration; and 2) a 7 ml draw 3 hr (+/-15min) post NT-I7 administration. Only one PK blood draw is performed at Cycle 1 Week 1 and EOT.

12. MEASUREMENT OF EFFECT

Although the clinical benefit of NT-I7 in HIV-positive and HIV-negative patients with Kaposi Sarcoma (KS) 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.

12.1 Antitumor Effect – Kaposi sarcoma

For the purposes of this study, patients should be re-evaluated for response according to the schedule established in the study calendar (Section 11). Kaposi sarcoma will be evaluated using a modified version (consistent with NCI studies) of the AIDS Clinical Trial Group (ACTG) Oncology Committee staging and response definitions for KS (Assessment guidelines are provided in Appendix D).

It should be noted that there is some observer variability in the evaluation of the number, size, nodularity, and color of lesions, and this must be considered when measurements are interpreted.

For evaluation of less than complete responses in participants with more than 50 lesions at entry, only the previously selected 1-3 representative areas that contain at least 20 lesions will be considered. However, complete responses still require the absence of any detectable diseases over the entire body (i.e., not confined to the representative areas).

12.1.1 Methods of Evaluation for Measurable Disease

12.1.1.1 KS Tumor Photography

Whole body photographs will be obtained upon entry into the study and a time of change in response (i.e. determination of partial or complete response or time of progressive disease) as well as at the end of the study. At these time points, 5 lesions (hereafter called marker lesions), representative of the patient's disease and, if possible, located on separate areas of the body will be selected. These marker lesions should be lesions that have never been treated with local therapies such as radiation therapy or intralesional injections. An attempt will be made to distribute the "marker" lesions between the representative areas and the rest of the body. Detailed photographs of these lesions will be obtained with a metric ruler beside them.

12.1.1.2 Documentation of Marker Lesions

The size, color and nodularity of the marker lesions will be recorded. Documentation will depend on the number of lesions.

12.1.1.3 Documentation of Extent of Disease

12.1.1.3.1 Subjects with 50 or more KS lesions

For subjects with 50 or more lesions at entry, between 1 and 3 representative areas will be selected at baseline and these will be used for each subsequent evaluation. Representative areas are sections of the body (e.g. the back, a leg, an arm, etc.), which contain at least 20 KS lesions.

The total number of lesions in these representative areas will be counted and a record made of whether they are flat or raised. If, in the course of treatment, a single lesion breaks up into 2 or more smaller lesions whose area does not extend beyond the boundary of the initial lesion, these lesions will still be counted as single lesions for the purpose of assessing total numbers in defining a response to therapy.

12.1.1.3.2 Subjects with fewer than 50 KS lesions

For subjects with less than 50 lesions at entry, the total number of lesions will be counted, and a record made of whether they are flat or raised.

12.1.1.3.3 Additional studies for visceral KS involvement

Additional studies, including but not limited to, gastrointestinal endoscopy and bronchoscopy will be performed at baseline where clinically indicated, based on clinical evaluation of the patient.

12.1.2 Kaposi sarcoma Response Criteria

12.1.2.1 Complete Response

The absence of any detectable residual disease, including tumor associated edema, persisting for at least 4 weeks.

- For subjects with pigmented macular skin lesions persisting after apparent complete response, a biopsy of at least one representative lesion is required to document the absence of malignant cells. If a lesion has not been biopsied, the patient may be classified as having a clinical CR.

- For subjects with visceral disease, the diagnostic radiologic or endoscopic study should be repeated if not medically contraindicated and found to be negative for evidence of disease. If such procedures are medically contraindicated but the patient has no clinical evidence of visceral disease, the patient may be classified as having a clinical CR.

12.1.2.2 Clinical Complete Response

The absence of any detectable residual disease, including tumor associated edema, persisting for at least 4 weeks.

- For subjects with pigmented macular skin lesions persisting after apparent complete response, if a representative lesion has not been biopsied.

- For subjects with visceral disease, the diagnostic radiologic or endoscopic study should be repeated if not medically contraindicated and found to be negative for evidence of disease. If such procedures are medically contraindicated but the patient has no clinical evidence of visceral disease, the patient may be classified as having a clinical CR.

12.1.2.3 Partial Response

No progressive disease (see below and noting, that single lesions which split up into 2 or more smaller lesions during the course of treatment will still be counted as one); no new lesions occurring in previously uninvolved areas of the body; no new visceral sites of involvement or the appearance or worsening of tumor-associated edema or effusions *and*:

- A 50% or greater decrease in the number and/or size of previously existing lesions **lasting for at least 4 weeks** *or*
- Complete flattening of at least 50% of all previously raised lesions (i.e., 50% of all previously nodular or plaque-like lesions become macular) **lasting for at least 4 weeks** *or*
- A 50% decrease in radiologically measurable visceral lesions sustained without evidence of re-growth **for at least 4 weeks** *or*
- A 50% decrease in radiologically measurable visceral lesions sustained without evidence of re-growth **for at least 4 weeks** *or*
- Subjects who otherwise meet the criteria for a CR but still have residual tumor-associated edema or effusions will be classified as having a PR.

12.1.2.4 Progressive Disease

For those criteria that involve measurement of lesions in the clinic, the designation of progression should be made, when feasible, only when the criteria below have been **met in two measurements spaced at least 1 week apart**. For the assignment of progressive disease for the primary outcome analysis, progression will be defined in comparison to baseline measurements.

- An increase of 25% or more over baseline in the number of lesions and/or the size (sum of the products of the largest perpendicular diameters) of the marker lesions *or*
- A change in character from macular to plaque-like or nodular of at least 25% of the lesions *or*
- New visceral sites of involvement or progression of visceral disease *or*
- The development of new or increasing tumor-associated edema or effusion that lasts at least 1 week and interferes with the patient's normal activities.

12.1.2.5 Stable Disease

Any tumor measurement not meeting the criteria for Complete Response, Partial Response or Progressive Disease.

13. STUDY OVERSIGHT AND DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 10 (Adverse Events: List and Reporting Requirements).

13.1 Study Oversight

This protocol is monitored at several levels, as described in this section. The Protocol PI is responsible for monitoring the conduct and progress of the clinical trial, including the ongoing review of accrual, patient-specific clinical and laboratory data, and routine and serious AEs; reporting of expedited AEs; and accumulation of reported AEs from other trials testing the same drug. The Protocol PI and statistician have access to the data at all times.

All decisions regarding dose escalation/expansion/de-escalation require sign-off by the Protocol PI. In addition, the Protocol PI will have at least monthly, or more frequently, conference calls with the Study Investigators to review accrual, progress, and adverse events and unanticipated problems.

All Study Investigators at participating sites who register/enroll patients on a given protocol are responsible for timely submission of data via Medidata Rave and timely reporting of AEs for that particular study. This includes timely review of data collected on the electronic CRFs submitted via Medidata Rave.

All studies are also reviewed in accordance with the enrolling institution's data safety monitoring plan.

13.2 Data Reporting

Medidata Rave is a clinical data management system being used for data collection for this trial/study. Access to the trial in Rave is controlled through the CTEP-IAM system and role assignments.

Requirements to access Rave via iMedidata:

- A valid CTEP-IAM account; and
- Assigned a Rave role on the LPO or PO roster at the enrolling site of: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator.

Rave role requirements:

- Rave CRA or Rave CRA (Lab Admin) role must have a minimum of an Associate Plus (AP) registration type;
- Rave Investigator role must be registered as an Non-Physician Investigator (NPIVR) or Investigator (IVR); and

- Rave Read Only role must have at a minimum an Associates (A) registration type.

Refer to https://ctep.cancer.gov/investigatorResources/default.htm for registration types and documentation required.

This study has a Delegation of Tasks Log (DTL). Therefore, those requiring write access to Rave must also be assigned the appropriate Rave tasks on the DTL.

Upon initial site registration approval for the study in Regulatory Support System (RSS), all persons with Rave roles assigned on the appropriate roster will be sent a study invitation email from iMedidata. To accept the invitation, site staff must either click on the link in email or log in to iMedidata via the CTSU members' website under *Data Management* > *Rave Home* and click to *accept* the invitation in the *Tasks* pane located in the upper right-corner of the iMedidata screen. Site staff will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings) and can be accessed by clicking on the eLearning link in the *Tasks* pane located in the upper right corner of the iMedidata screen. If an eLearning is required for a study and has not yet been taken, the link to the eLearning will appear under the study name in the *Studies* pane located in the center of the iMedidata screen; once the successful completion of the eLearning has been recorded, access to the study in Rave will be granted, and a *Rave EDC* link will replace the eLearning link under the study name.

Site staff that have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website in the Data Management section under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website in the Data Management > Rave section at www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at 1-888-823-5923 or by email at ctsucontact@westat.com.

13.2.1 Method

This study will be monitored by the Clinical Trials Monitoring Service (CTMS). Data will be submitted to CTMS at least once every two weeks via Medidata Rave (or other modality if approved by CTEP). Information on CTMS reporting is available at http://www.theradex.com/clinicalTechnologies/?National-Cancer-Institute-NCI-11. On-site audits will be conducted three times annually (one annual site visit and two data audits). For CTMS monitored studies, after users have activated their accounts, please contact the Theradex Help Desk at (609) 619-7862 or by email at CTMSSupport@theradex.com for additional support with Rave and completion of CRFs

13.2.2 Responsibility for Data Submission

Data are to be submitted via Medidata Rave to CTMS on a real-time basis, but no less than once every 2 weeks. The timeliness of data submissions and timeliness in resolving data queries will be tracked by CTMS. Metrics for timeliness will be followed and assessed on a quarterly basis.

For the purpose of Institutional Performance Monitoring, data will be considered delinquent if it is greater than 4 weeks past due.

Data from Medidata Rave and CTEP-AERS is reviewed by the CTMS on an ongoing basis as data is received. Queries will be issued by CTMS directly within Rave. The queries will appear on the Task Summary Tab within Rave for the CRA at the ETCTN to resolve. Monthly web-based reports are posted for review by the Drug Monitors in the IDB, CTEP. Onsite audits will be conducted by the CTMS to ensure compliance with regulatory requirements, GCP, and NCI policies and procedures with the overarching goal of ensuring the integrity of data generated from NCI-sponsored clinical trials, as described in the ETCTN Program Guidelines, which may be found on the CTEP (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm) and CTSU websites.

CTMS will utilize a core set of eCRFs that are Cancer Data Standards Registry and Repository (caDSR) compliant (http://cbiit.nci.nih.gov/ncip/biomedical-informatics-resources/interoperability-and-semantics/metadata-and-models). Customized eCRFs will be included when appropriate to meet unique study requirements. The PI is encouraged to review the eCRFs, working closely with CTMS to ensure prospectively that all required items are appropriately captured in the eCRFs prior to study activation. CTMS will prepare the eCRFs with built-in edit checks to the extent possible to promote data integrity.

13.3 Data Quality Portal

The Data Quality Portal (DQP) provides a central location for site staff to manage unanswered queries and form delinquencies, monitor data quality and timeliness, generate reports, and review metrics.

The DQP is located on the CTSU members' website under Data Management. The Rave Home section displays a table providing summary counts of Total Delinquencies and Total Queries. DQP Queries, DQP Delinquent Forms, DQO Form Status and the DQP Reports modules are available to access details and reports of unanswered queries, delinquent forms, forms with current status and timeliness reports. Review the DQP modules on a regular basis to manage specified queries and delinquent forms.

The DQP is accessible by site staff that are rostered to a site and have access to the CTSU website. Staff that have Rave study access can access the Rave study data using a direct link on the DQP.

To learn more about DQP use and access, click on the Help icon displayed on the Rave Home, DQP Queries, DQP Delinquent Forms, DQP Form Status, and DQP Reports modules.

13.4 CTEP Multicenter Guidelines

This protocol will adhere to the policies and requirements of the CTEP Multicenter Guidelines. The specific responsibilities of the PI and the Coordinating Center (Study Coordinator) and the procedures for auditing are presented in Appendix C.

- The Principal Investigator/Coordinating Center is responsible for distributing all IND Action Letters or Safety Reports received from CTEP to all participating institutions for submission to their individual IRBs for action as required.

13.5 Genomic Data Sharing Plan: N/A

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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.

APPENDIX B NT-I7 INTRAMUSCULAR INJECTION GUIDELINES

NT-I7 dose will be determined using the subject's body weight obtained prior to IP administration. NT-I7 dose must be re-assessed if the subject's weight changes +/- 10% from the baseline weight measurement.

For non-obese subjects (BMI < 30kg/m^2), dosing is determined by actual body weight and dosing/injection volume chart listed below.

For obese subjects (BMI ≥ 30kg/m^2), dosing will be determined by adjusted body weight (see below formula).
If BMI ≥ 30kg/m^2, proceed with the following steps:

1. Determine Ideal Weight (1 kg = 2.2 lbs):

Males: *50 kg + 2.3 kg × (inches over 5 feet)*
Females: *45.5 kg + 2.3 kg × (inches over 5 feet)*
(Subjects less than 5 feet: subtract 2.3 kg/inches under 5 feet)

2. Determine Adjusted Body Weight:

Ideal Weight + 0.4 × (Actual Weight – Ideal Weight) = Adjusted Body Weight (ABW)

For obese subjects, apply ABW calculation from the above formula, and calculate appropriate dose from the NT-I7 dosing and injection volume chart listed below.

The following criteria should be used for rounding weight in kg to the nearest whole number for final NT-I7 dose calculation:

1. If the tenths digit is equal or above 5, then round up to the whole number. For example, weight measurement of 73.8 kg would be rounded up to 74 kg.
2. If the tenths digit is below 5, round down to the whole number. For example, weight measurement of 73.4 kg would be rounded down to 73kg.

Dose and Injection Volume Chart

Body wt.	**240 µg/kg (DL-2)**			**360 µg/kg (DL-1)**			**480 µg/kg (DL 1)**		
(kg)	**25 mg/mL**			**25 mg/mL**			**25 mg/mL**		
	Dose (mg)	**Vol (mL)**	**# of NT-I7 vials for preparation**	**Dose (mg)**	**Vol (mL)**	**# of NT-I7 vials for preparation**	**Dose (mg)**	**Vol (mL)**	**# of NT-I7 vials for preparation**
50	12.00	0.48	1	18.00	0.72	1	24.00	0.96	1
51	12.24	0.49	1	18.36	0.73	1	24.48	0.98	1
52	12.48	0.50	1	18.72	0.75	1	24.96	1.00	1
53	12.72	0.51	1	19.08	0.76	1	25.44	1.02	2
54	12.96	0.52	1	19.44	0.78	1	25.92	1.04	2
55	13.20	0.53	1	19.80	0.79	1	26.40	1.06	2

56	13.44	0.54	1	20.16	0.81	1	26.88	1.08	2
57	13.68	0.55	1	20.52	0.82	1	27.36	1.09	2
58	13.92	0.56	1	20.88	0.84	1	27.84	1.11	2
59	14.16	0.57	1	21.24	0.85	1	28.32	1.13	2
60	14.40	0.58	1	21.60	0.86	1	28.80	1.15	2
61	14.64	0.59	1	21.96	0.88	1	29.28	1.17	2
62	14.88	0.60	1	22.32	0.89	1	29.76	1.19	2
63	15.12	0.60	1	22.68	0.91	1	30.24	1.21	2
64	15.36	0.61	1	23.04	0.92	1	30.72	1.23	2
65	15.60	0.62	1	23.40	0.94	1	31.20	1.25	2
66	15.84	0.63	1	23.76	0.95	1	31.68	1.27	2
67	16.08	0.64	1	24.12	0.96	1	32.16	1.29	2
68	16.32	0.65	1	24.48	0.98	1	32.64	1.31	2
69	16.56	0.66	1	24.84	0.99	1	33.12	1.32	2
70	16.80	0.67	1	25.20	1.01	2	33.60	1.34	2
71	17.04	0.68	1	25.56	1.02	2	34.08	1.36	2
72	17.28	0.69	1	25.92	1.04	2	34.56	1.38	2
73	17.52	0.70	1	26.28	1.05	2	35.04	1.40	2
74	17.76	0.71	1	26.64	1.07	2	35.52	1.42	2
75	18.00	0.72	1	27.00	1.08	2	36.00	1.44	2
76	18.24	0.73	1	27.36	1.09	2	36.48	1.46	2
77	18.48	0.74	1	27.72	1.11	2	36.96	1.48	2
78	18.72	0.75	1	28.08	1.12	2	37.44	1.50	2
79	18.96	0.76	1	28.44	1.14	2	37.92	1.52	2
80	19.20	0.77	1	28.80	1.15	2	38.40	1.54	2
81	19.44	0.78	1	29.16	1.17	2	38.88	1.56	2
82	19.68	0.79	1	29.52	1.18	2	39.36	1.57	2
83	19.92	0.80	1	29.88	1.20	2	39.84	1.59	2
84	20.16	0.81	1	30.24	1.21	2	40.32	1.61	2
85	20.40	0.82	1	30.60	1.22	2	40.80	1.63	2
86	20.64	0.83	1	30.96	1.24	2	41.28	1.65	2
87	20.88	0.84	1	31.32	1.25	2	41.76	1.67	2
88	21.12	0.84	1	31.68	1.27	2	42.24	1.69	2
89	21.36	0.85	1	32.04	1.28	2	42.72	1.71	2
90	21.60	0.86	1	32.40	1.30	2	43.20	1.73	2
91	21.84	0.87	1	32.76	1.31	2	43.68	1.75	2
92	22.08	0.88	1	33.12	1.32	2	44.16	1.77	2
93	22.32	0.89	1	33.48	1.34	2	44.64	1.79	2
94	22.56	0.90	1	33.84	1.35	2	45.12	1.80	2
95	22.80	0.91	1	34.20	1.37	2	45.60	1.82	2
96	23.04	0.92	1	34.56	1.38	2	46.08	1.84	2

97	23.28	0.93	1	34.92	1.40	2	46.56	1.86	2
98	23.52	0.94	1	35.28	1.41	2	47.04	1.88	2
99	23.76	0.95	1	35.64	1.43	2	47.52	1.90	2
100	24.00	0.96	1	36.00	1.44	2	48.00	1.92	2
101	24.24	0.97	1	36.36	1.45	2	48.48	1.94	2
102	24.48	0.98	1	36.72	1.47	2	48.96	1.96	2
103	24.72	0.99	1	37.08	1.48	2	49.44	1.98	2
104	24.96	1.00	1	37.44	1.50	2	49.92	2.00	2
105	25.20	1.01	2	37.80	1.51	2	50.40	2.02	3
106	25.44	1.02	2	38.16	1.53	2	50.88	2.04	3
107	25.68	1.03	2	38.52	1.54	2	51.36	2.05	3
108	25.92	1.04	2	38.88	1.56	2	51.84	2.07	3
109	26.16	1.05	2	39.24	1.57	2	52.32	2.09	3
110	26.40	1.06	2	39.60	1.58	2	52.80	2.11	3
111	26.64	1.07	2	39.96	1.60	2	53.28	2.13	3
112	26.88	1.08	2	40.32	1.61	2	53.76	2.15	3
113	27.12	1.08	2	40.68	1.63	2	54.24	2.17	3
114	27.36	1.09	2	41.04	1.64	2	54.72	2.19	3
115	27.60	1.10	2	41.40	1.66	2	55.20	2.21	3
116	27.84	1.11	2	41.76	1.67	2	55.68	2.23	3
117	28.08	1.12	2	42.12	1.68	2	56.16	2.25	3
118	28.32	1.13	2	42.48	1.70	2	56.64	2.27	3
119	28.56	1.14	2	42.84	1.71	2	57.12	2.28	3
120	28.80	1.15	2	43.20	1.73	2	57.60	2.30	3

Dose and Injection Volume Chart (cont.)

Body wt	960 µg/kg (DL 2)			1200 µg/kg (DL 3)		
(kg)	25 mg/mL			25 mg/mL		
	Dose (mg)	Vol (mL)	# of NT-I7 vials for preparation	Dose (mg)	Vol (mL)	# of NT-I7 vials for preparation
50	48.00	1.92	2	60.00	2.40	3
51	48.96	1.96	2	61.20	2.45	3
52	49.92	2.00	2	62.40	2.50	3
53	50.88	2.04	3	63.60	2.54	3
54	51.84	2.07	3	64.80	2.59	3
55	52.80	2.11	3	66.00	2.64	3
56	53.76	2.15	3	67.20	2.69	3
57	54.72	2.19	3	68.40	2.74	3
58	55.68	2.23	3	69.60	2.78	3
59	56.64	2.27	3	70.80	2.83	3
60	57.60	2.30	3	72.00	2.88	3
61	58.56	2.34	3	73.20	2.93	3
62	59.52	2.38	3	74.40	2.98	3
63	60.48	2.42	3	75.60	3.02	4
64	61.44	2.46	3	76.80	3.07	4
65	62.40	2.50	3	78.00	3.12	4
66	63.36	2.53	3	79.20	3.17	4
67	64.32	2.57	3	80.40	3.22	4
68	65.28	2.61	3	81.60	3.26	4
69	66.24	2.65	3	82.80	3.31	4
70	67.20	2.69	3	84.00	3.36	4
71	68.16	2.73	3	85.20	3.41	4
72	69.12	2.76	3	86.40	3.46	4
73	70.08	2.80	3	87.60	3.50	4
74	71.04	2.84	3	88.80	3.55	4
75	72.00	2.88	3	90.00	3.60	4
76	72.96	2.92	3	91.20	3.65	4
77	73.92	2.96	3	92.40	3.70	4
78	74.88	3.00	3	93.60	3.74	4
79	75.84	3.03	4	94.80	3.79	4
80	76.80	3.07	4	96.00	3.84	4
81	77.76	3.11	4	97.20	3.89	4
82	78.72	3.15	4	98.40	3.94	4
83	79.68	3.19	4	99.60	3.98	4
84	80.64	3.23	4	100.80	4.03	5

85	81.60	3.26	4	102.00	4.08	5
86	82.56	3.30	4	103.20	4.13	5
87	83.52	3.34	4	104.40	4.18	5
88	84.48	3.38	4	105.60	4.22	5
89	85.44	3.42	4	106.80	4.27	5
90	86.40	3.46	4	108.00	4.32	5
91	87.36	3.49	4	109.20	4.37	5
92	88.32	3.53	4	110.40	4.42	5
93	89.28	3.57	4	111.60	4.46	5
94	90.24	3.61	4	112.80	4.51	5
95	91.20	3.65	4	114.00	4.56	5
96	92.16	3.69	4	115.20	4.61	5
97	93.12	3.72	4	116.40	4.66	5
98	94.08	3.76	4	117.60	4.70	5
99	95.04	3.80	4	118.80	4.75	5
100	96.00	3.84	4	120.00	4.80	5
101	96.96	3.88	4	121.20	4.85	5
102	97.92	3.92	4	122.40	4.90	5
103	98.88	3.96	4	123.60	4.94	5
104	99.84	3.99	4	124.80	4.99	5
105	100.80	4.03	5	126.00	5.04	6
106	101.76	4.07	5	127.20	5.09	6
107	102.72	4.11	5	128.40	5.14	6
108	103.68	4.15	5	129.60	5.18	6
109	104.64	4.19	5	130.80	5.23	6
110	105.60	4.22	5	132.00	5.28	6
111	106.56	4.26	5	133.20	5.33	6
112	107.52	4.30	5	134.40	5.38	6
113	108.48	4.34	5	135.60	5.42	6
114	109.44	4.38	5	136.80	5.47	6
115	110.40	4.42	5	138.00	5.52	6
116	111.36	4.45	5	139.20	5.57	6
117	112.32	4.49	5	140.40	5.62	6
118	113.28	4.53	5	141.60	5.66	6
119	114.24	4.57	5	142.80	5.71	6
120	115.20	4.61	5	144.00	5.76	6

Guidelines for Injecting NT-I7 Solution by Nurse or Investigator:

- With one hand, gently press the cleaned area of skin and hold it firmly. With the other hand, hold the syringe at about a 90º angle to the skin.
- With a quick, short motion, push the needle through the skin into the muscle.
- With your free hand, slowly push the plunger to inject solution. Inject 1mL per 10-15 seconds.
- When the syringe is empty, remove the needle from the skin being careful to keep it at the same angle it was when it was inserted.

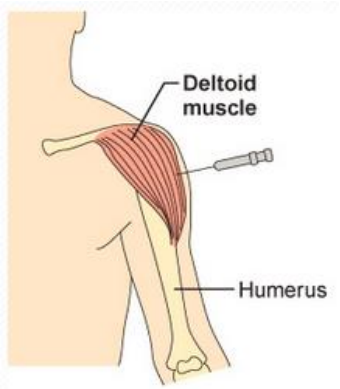
Press a cotton ball over the injection site for 10 seconds. Slight bleeding may occur. **DO NOT** rub the injection site. A bandage is optional.

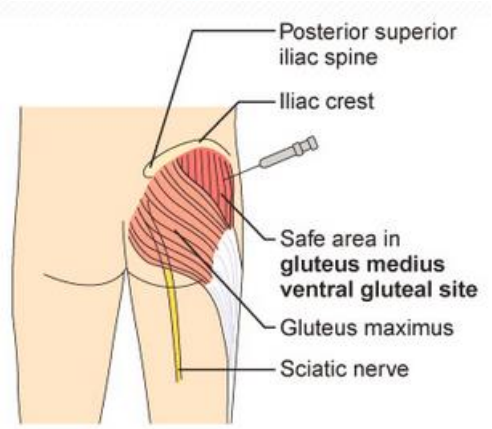
Injection Sites

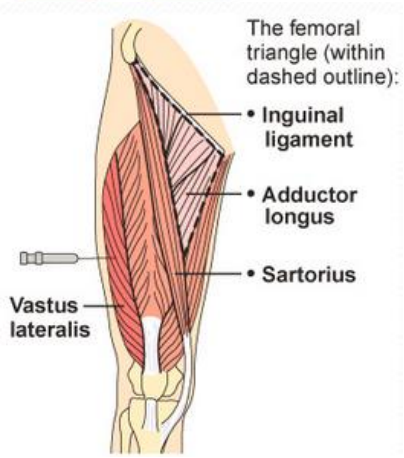
NT-I7 will be injected by intra-muscular route. The best areas for injection are the deltoid muscle and the muscles of the thighs and buttock; it should remain away from joints, nerves, bones, and other important structures.

Study drug injection areas are localized preferably on the arms, thighs, and buttocks. Do not use the same site for injection when the volume of injection requires several injections to a patient. **The maximum volume that may be administered per intramuscular injection is 1mL. Dose volumes greater than 1 mL should be divided into 2 or more injections.** Use the attached Injection Site Diary and the site codes below to document the injection site(s).

INTRAMUSCULAR INJECTION SITES







Left Deltoid “A”	Right Deltoid “B”
Left Buttock “C”	Right Buttock “D”
Left Thigh “E”	Right Thigh “F”

STUDY INJECTION SITE DIARY (to be completed by nurse or investigator)

Site Name/Number_____ Subject Study ID _____

IM Injections **NT-I7**	**Date of Dosing** (DD/MMM/YYYY) **Cycle =** **Day =**	**Protocol No. CITN-17** **IM Injection Site(s)**
#1		❒ A ❒ B ❒ C ❒ D ❒ E ❒ F
#2		❒ A ❒ B ❒ C ❒ D ❒ E ❒ F
#3		❒ A ❒ B ❒ C ❒ D ❒ E ❒ F
#4		❒ A ❒ B ❒ C ❒ D ❒ E ❒ F

APPENDIX C CTEP MULTICENTER GUIDELINES

If an institution wishes to collaborate with other participating institutions in performing a CTEP-sponsored research protocol, then the guidelines below must be followed.

Responsibility of the Protocol Chair

- The Protocol Chair will be the single liaison with the CTEP Protocol and Information Office. The Protocol Chair is responsible for the coordination, development, submission, and approval of the protocol as well as its subsequent amendments. The protocol must not be rewritten or modified by anyone other than the Protocol Chair. There will be only one version of the protocol, and each participating institution will use that document. The Protocol Chair is responsible for assuring that all participating institutions are using the correct version of the protocol.
- The Protocol Chair is responsible for the overall conduct of the study at all participating institutions and for monitoring its progress. All reporting requirements to CTEP are the responsibility of the Protocol Chair.
- The Protocol Chair is responsible for the timely review of Adverse Events (AE) to assure safety of the patients.
- The Protocol Chair will be responsible for the review of and timely submission of data for study analysis.

Responsibilities of the Coordinating Center

- Each participating institution will have an appropriate assurance on file with the Office for Human Research Protection (OHRP), NIH. The Coordinating Center is responsible for assuring that each participating institution has an OHRP assurance and must maintain copies of IRB approvals from each participating site.
- Prior to the activation of the protocol at each participating institution, an OHRP form 310 (documentation of IRB approval) must be submitted to the CTEP PIO.
- The Coordinating Center is responsible for central patient registration. The Coordinating Center is responsible for assuring that IRB approval has been obtained at each participating site prior to the first patient registration from that site.
- The Coordinating Center is responsible for the preparation of all submitted data for review by the Protocol Chair.
- The Coordinating Center will maintain documentation of AE reports. There are two options for AE reporting: (1) participating institutions may report directly to CTEP with a copy to the Coordinating Center, or (2) participating institutions report to the Coordinating Center who in turn report to CTEP. The Coordinating Center will submit AE reports to the Protocol Chair for timely review.
- Audits may be accomplished in one of two ways: (1) source documents and research records for selected patients are brought from participating sites to the Coordinating Center for audit, or (2) selected patient records may be audited on-site at participating sites. If the NCI chooses to have an audit at the Coordinating Center, then the Coordinating Center is responsible for having all source documents, research records, all IRB approval documents, NCI Drug Accountability Record forms, patient registration

lists, response assessments scans, x-rays, *etc.*, available for the audit.

Inclusion of Multicenter Guidelines in the Protocol

- The protocol must include the following minimum information:
  - The title page must include the name and address of each participating institution and the name, telephone number and e-mail address of the responsible investigator at each participating institution.
  - The Coordinating Center must be designated on the title page.
  - Central registration of patients is required. The procedures for registration must be stated in the protocol.
  - Data collection forms should be of a common format. Sample forms should be submitted with the protocol. The frequency and timing of data submission forms to the Coordinating Center should be stated.
  - Describe how AEs will be reported from the participating institutions, either directly to CTEP or through the Coordinating Center.
  - Describe how Safety Reports and Action Letters from CTEP will be distributed to participating institutions.

Agent Ordering

- Except in very unusual circumstances, each participating institution will order DCTD-supplied investigational agents directly from CTEP. Investigational agents may be ordered by a participating site only after the initial IRB approval for the site has been forwarded by the Coordinating Center to the CTEP PIO.

APPENDIX D KS CUTANEOUS AND ORAL EXAM AND EVALUATION KS RESPONSE

1. Kaposi's Sarcoma Examination

1.1. Kaposi's Sarcoma Entry Examination

Timing - The KS entry examination should be performed prior to receiving study medication but no earlier than 2 weeks before initiating treatment. Tumor measurements should include the following:

A. Identify and Measure Cutaneous Marker Lesions

Select Marker Lesions
Select bi-dimensionally measurable marker lesions for assessing changes in lesion dimensions. Select the largest lesions with clearly defined margins. When available, a minimum of five bi-dimensionally measurable KS cutaneous marker lesions should be selected. If fewer than five bi-dimensionally measurable marker lesions are available, the total surface area of the marker lesion(s) should be ≥700mm². To facilitate repeated lesion measurements, the location of each marker lesion should be described in the Marker Lesion Table, recorded on the standard body diagram (Page 3 of Response Sheet, Appendix E) in relation to body landmarks and other nearby lesions and photographed as described in Section 3.

> ***Note:*** Lesions used as marker lesions for measuring response to treatment should NOT be the lesions chosen for biopsies for Tumor Marker Assessments.

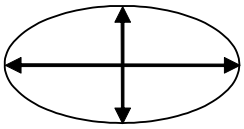
Measure Marker Lesions
Each marker lesion should be measured in millimeters, indicating the longest linear dimension and the longest dimension perpendicular to it. For this protocol, the product of the largest perpendicular diameters of the marker lesion will be considered the AREA of the marker lesion. Please refer to the diagrams below:

Next, calculate the sum of the products of the areas of the indicator lesion(s).

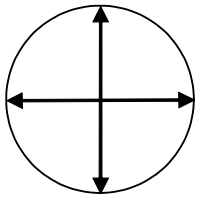
The sum calculated at entry or at the best response will be used to determine the response status at follow-up visits.

Calculate and Record Thresholds from Baseline for Partial Response and Progressive Disease.

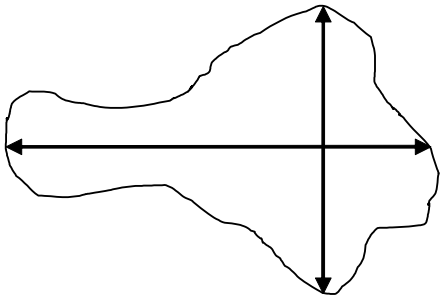
Examples of calculating the **area** of the indicator lesions



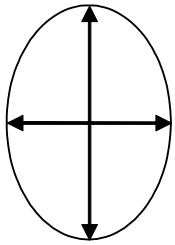
Oval Lesion: 35mm X 16mm = 560 mm²



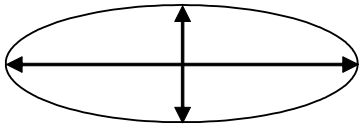
Round Lesion: 25mm X 25mm = 625 mm²



Irregular Lesion: 57mm X 39mm = 2223 mm²



Oval Lesion: 32mm X 22mm = 704 mm²



Oval Lesion: 47mm X 16mm = 752 mm²

Next, calculate the sum of the products of the areas of the indicator lesion(s).

To calculate the **sum of the areas** of the 5 example indicator lesions above, simply add the areas of each lesion:

560 mm² + 625 mm² + 2223 mm² + 704 mm² + 752 mm² = 4864 mm²

Using the five marker lesions above, the sum of the areas is 4864 mm².

The sum calculated at entry or at the best response will be used to determine the response status at follow-up visits.

Calculate and Record Thresholds from Baseline for Partial Response and Progressive Disease

Partial Response threshold = Total product x 0.5
Progressive Disease threshold = Total Product x 1.25

Record Product thresholds on Page 1 of the Response Sheet.

B. Evaluate Lesion Number (Total and Nodular/Raised)

Select Representative Areas
For participants with ≤50 total skin lesions, all lesions should be evaluated for changes in number and characteristics. For participants with >50 total skin lesions, choose three representative areas, if possible, for evaluating change in lesion numbers and characteristics (preferably each selected representative area should have at least 5 lesions, and the total number of lesions counted should be at least 20). **If it is not practical to choose three representative areas, the number of areas selected is left to the investigator's clinical judgment.** On Measurement worksheet, note if greater than 50 lesions.

> ***Note:*** A representative area is a single extremity, the back, chest, or face that has lesions similar in characteristics, i.e., nodularity, size, color, and number, to those found on other parts of the body. A representative area does not need to be the area with the largest number of lesions but should contain lesions that are truly representative of those throughout the remainder of the body. **Confluent lesions should be avoided when possible.**

Lesion Count (Nodular/raised and Flat)
The total number of nodular/raised and flat lesions (either total body or in the representative area(s)) must be counted. Use the Lesion Count tally sheet on Page 1 of the Response Sheet. Label body area counted, and use separate columns for Nodular and Flat lesions. Consider using a pen to mark lesions on skin as they are counted to aid. Mark the area counts and totals on Page 1 on the Response Sheet.

C. Evaluate Edema

On page 2 of the Response Sheet, record the presence or absence of tumor-associated the severity of edema, and the location of tumor-associated edema, if present.

In addition, lower extremity edema should be measured. Measure the circumference, in centimeters, of the ankle at the level of the malleoli and of the calf at a point 10 cm below the lower border of the patella. This must be done at entry in all participants whether there is edema or not. For patients with lower extremity edema, consider also documenting edema at the level of the thigh and pelvis. For each measurement, note the distance from an anatomical landmark.

D. Perform Oral Examination

An oral mucosal tissue examination will be conducted on all study participants to detect the presence of oral cavity KS lesions.

The recommended standardized oral mucosal tissue examination should be conducted wearing gloves and 2x2 inch gauze and light. The oral examination should be conducted in the following sequence:

Lips
Begin examination by observing the lips, with the mouth both closed and opened. Note the color, texture, and any surface abnormalities of the upper and lower lip.

Labial Mucosa
With the mouth partially open, visually examine the lower labial mucosa by pulling the lower lip and stretching it over the chin, holding it between your thumb and index finger and using both hands. Repeat the same steps for the examination of the upper labial mucosa by pulling the upper lip and stretching it over the nose.

Buccal Mucosa and Vestibules
With the mouth open wide, examine first the right buccal mucosa (inside of cheek) extending from the labial commissures (corner of the lips) and back to the anterior tonsilar pillar. Examine both the upper and lower vestibule using the mirror to stretch the buccal mucosa and to help visualize the posterior vestibules. Examine the left buccal mucosa, following the same guidelines.

Hard and Soft Palate
With the mouth wide open and the participant's head tilted backwards, inspect the hard palate (note the ridges or rugae) located in the anterior part, and then the soft palate and uvula (ask the participant to say "ahhh" to better visualize the soft palate).

Tongue
With the participant's tongue at rest and mouth partially open, inspect the dorsum of the tongue for any swelling, ulceration, coating or variation in size, color, or texture. Also note any change in the pattern of the papillae covering the surface of the tongue and examine the top and the tip of the tongue. The participant should then protrude the tongue, and the examiner should gasp the tip of the tongue with a piece of gauze to assist with full protrusion and allow examination of the margins or lateral borders. Note the small "lumps" located on each side of the posterior lateral tongue in the base of tongue area; these are the

foliate papillae (considered to be an extension of the lingual tonsils). Then observe the ventral surface.

Floor of Mouth
With the tongue still elevated, inspect the floor of the mouth for swellings or other abnormalities.

Gingiva
First, examine the buccal and labial aspects of the gingiva and alveolar ridge. Start with the right maxillary posterior gingiva and alveolar ridge and move around the arch to the left posterior gingiva. Continue with the left mandibular posterior gingiva and alveolar ridge and move around the arch to the right posterior gingiva.

Second, examine the palatal and lingual aspects as has been done on the facial side, from right to left on the palatal (maxilla) and left to right on the lingual (mandible). Use the mouth mirror to retract the posterior part of the tongue and focus the light to better visualize the lingual gingiva.

Record the presence or absence of oral cavity KS lesions and their location on Page 1 of the Worksheet. Note whether lesions are raised or flat.

E. Evaluating Disease that cannot be Measured by Physical Exam (Evaluable Disease, Visceral KS)

Screening and Follow up for Visceral Disease
A chest X-ray (CXR) will be performed at screening. If the CXR findings are abnormal, additional evaluations are required in consultation with a pulmonologist. Bronchoscopy with visualization of lesions consistent with Kaposi sarcoma or lung biopsy are required for documentation of pulmonary KS. Appropriate microbiologic evaluation to exclude infectious etiologies is required. If pulmonary KS is noted, a CT scan should be performed to document disease.

At screening, potential study participants must be asked about the presence of gastrointestinal (GI) symptoms (odynophagia, nausea, vomiting, rectal bleeding, and/or abdominal pain). **If GI symptoms are present or microcytic anemia are noted at baseline, further evaluations should include stool tests for occult blood and infectious etiologies if infection is suspected.** Consultation with a gastroenterologist for upper and/or lower GI endoscopy is recommended in cases of occult blood loss or unexplained gastrointestinal symptoms. Documentation of gastrointestinal KS requires direct visualization of pigmented lesion(s) consistent with KS on endoscopy (with or without biopsy confirmation).

Other Sites of Disease
CT scanning is not required at baseline in patients without other indications for a CT scan. If performed, KS involving other visceral organs or lymph nodes may be detected by advanced imaging techniques (e.g., CT or MRI scan, ultrasound) and confirmed by biopsy. If KS is

confirmed by biopsy in visceral organs, this information should be recorded. If there is an unconfirmed abnormality on a scan or ultrasound, and KS cannot be confirmed by biopsy, that information should be recorded and the abnormality followed during study treatment to determine if it changes.

Note presence of visceral lesions on page 1 of the Worksheet.

Evaluable Disease

Evaluable disease (also known as non-measurable disease) is disease that cannot be measured directly by the size of the tumor but can be evaluated by other methods. For purposes of this study, lesions considered truly non-measurable include: ascites, pleural or pericardial effusions, lymphangitic lung disease, abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques, bone lesions without an identifiable soft tissue component that can be evaluated by cross-sectional imaging techniques, and lesions that can be identified only by endoscopic, bronchoscopic, or laparoscopic techniques. Changes in the size of other types of disease may not be accurately quantifiable, for example discrete lung lesions on chest x-ray.

Effusions, when noted, should be evaluated to exclude primary effusion lymphoma whenever feasible before starting therapy.

For purposes of response assessment, the evaluation of non-measurable disease is used primarily to determine whether an individual has shown tumor progression when evaluation of measurable disease (i.e., cutaneous marker lesions, lesion counts, numbers of raised and flat lesions, edema, visceral disease that is measurable in two dimensions on CT scan) indicates response or stable disease. We will use the standard of "unequivocal progression", i.e., an overall level of substantial worsening of disease that is of a magnitude that, even in the presence of stable disease or partial response in measurable disease, the treating physician would feel it important to change therapy. This requires clinical judgment on the part of the investigator. For further guidance on the evaluation of non-measurable disease, please refer to the following:
Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 2000; 92(3):205-216.

The KS follow-up examination will be performed according to the schedule of events. Tumor evaluation should follow the guidelines noted in Section 1.1 above, and include:

- Record measurements of the longest linear dimension in millimeters and the longest dimension perpendicular to it of the same marker lesion(s) selected at entry;
- Record the total number of raised and flat lesions (in the same areas that were evaluated at entry, either total body or the representative area(s) selected at entry);
- Record the location, size, or characteristics of oral cavity lesions, after the oral mucosal tissue examination is conducted in the same sequence as the oral examination at entry;

- Record the severity of edema and the location of tumor-associated edema. If no edema was present at entry and no edema is present on the follow-up visit, repeat measurements are not required. If there was no edema at entry and edema develops at a follow-up visit, a re-measure at each KS follow-up evaluation is required. If edema was noted at entry, a re-measure at each KS follow-up evaluation is required.
- Record changes of visceral KS at the intervals required by the protocol if visceral disease was present at entry, or if symptoms suggesting visceral disease develop.

2. Calculating Response Status

Response status will be classified as complete response **(CR),** partial response **(PR),** stable disease, or progressive disease **(PD).** For a detailed definition of the KS response status, please refer Section 12.3 of the protocol, as well as reference article provided.

Response should be calculated from Baseline. For patients with decreasing tumor area or lesion counts, new thresholds should also be calculated for values at best response and used as a reference for comparison to subsequent values. **Document Response for Baseline and Response from additional time points (by Date or cycle number) on Page 2 of the Response Sheet.**

2.1 Calculate Response Status Based on Area of Marker Lesion(s)

To calculate the KS response status **based on area of marker lesions** you will need the area of the indicator lesions from entry. Next, calculate the area of the same indicator lesion(s) for the current visit. Subtract the area at the current visit from the area at entry, then divide this difference by the area at entry. **Multiplying by 100%** will give you the percentage change from entry. After a participant has had a **confirmed CR** or **PR**, subsequent measurements for PD should also be compared with the "best response" seen at a previous visit.

An initial confirmed PR is a ≥50% decrease in the area of the indicator lesion(s) compared to entry lasting for at least 4 weeks. For example, if a participant had an area of the indicator lesions of 4000mm² at entry and an area of the indicator lesions of 2000mm² at week 3, and this decrease was maintained for at least 4 weeks, the participant would have a **confirmed PR.**

PD is considered a ≥ 25% increase in the area of the indicator lesion(s) compared to entry or best response. For example, if the same participant as in the example above had an area of the indicator lesions of 5000mm² at week 3, the participant would have PD. Similarly, if a participant had an area of the indicator lesions of 4000mm² at entry and an area of the indicator lesions of 2000mm² at week 9 **that lasted for four weeks** (a **confirmed PR**) but at a subsequent visit was found have an area of 3000mm2 (a greater than 25% increase over the best response), the participant would have PD. **PD after a confirmed CR is defined by the presence of any KS following that confirmed CR.**

Note: **If a confirmed CR has been achieved and subsequent evaluations do not meet criteria for CR, this would be reported as PD.**

Please note that "best response" may improve after the initial **confirmed PR** is documented. For example, if the **entry** area of the indicator lesions was 5000mm² and the area decreased to 2400mm² at weeks **9 and 15**, this would be the initial **confirmed PR**. If, at week 18, the area of the indicator lesions decreased further to 2000mm², **then 2000mm2 is the new "best response". In this example, subsequent assessments of PD for the area of indicator lesions would be with respect to the number 2000mm², not to 2400mm². Thus, if the area of the indicator lesions at week 24 increased from 2000 to 2500mm2, this increase would constitute PD, despite the fact that 2500mm2 is 50% smaller than the entry lesion area.**

Note: **If a confirmed PR has been achieved and subsequent evaluations do not meet criteria for PD or CR, this would continue to be reported as PR. In the example above, if the entry area of the indicator lesions was 5000mm² and the area decreased to 2400mm² at weeks 9 and 15, and remained at 2400mm² at week 18, 2400mm² is the "best response" to date. If, at week 24, the area of the indicator lesions increased to 2800mm² this would continue to be reported as a PR because 2800 is less than a 25% increase from 2400. Similarly, if at week 24, the area of the indicator lesions decreased by an additional 10% to 2160mm², this would also continue to be reported as a PR.**

2.2 Calculate Response Status Based on the Number of Lesions

To calculate the response status based on the total number of lesions, you will need the total number of lesions (either whole body or, in the case of participants with over 50 lesions at entry, in the combined representative areas) from the entry KS exam. After an initial **confirmed CR** or **PR**, the percentage change for PD should be calculated from the "best response" seen at a previous visit.

An initial confirmed PR is a 50% or greater decrease in the number of lesions present at entry (either whole body or, in the case of participants with over 50 lesions at entry, in the combined representative areas) lasting for at least 4 weeks. For example, if a participant had 40 lesions at entry and had only 20 lesions at follow-up and this decrease was maintained for at least 4 weeks, that participant would have a **confirmed PR**.

For participants with ≤50 cutaneous lesions **at entry,** PD is defined as ≥25% increase in the total lesion count or a minimum of five new lesions, **whichever is greater**, compared to entry or best response. For example, if a participant had 35 lesions at entry and has 44 at follow-up, that would be classified as PD. **PD after a confirmed CR is defined by the presence of any KS following that confirmed CR.**

Note: **If a confirmed CR has been achieved and subsequent evaluations do not meet criteria for CR, this would be reported as PD.**

For participants with >50 cutaneous lesions **at entry**, PD is defined as ≥25% increase in the total number of lesions **or a minimum of five new lesions, whichever is greater,** in the combined prospectively-defined anatomic sites containing representative lesions **compared**

to entry or best response, or a total of five new lesions in anatomic sites which were previously documented as having no evidence of cutaneous disease. For example, if a participant had a total of 40 lesions at entry on the back and the right leg and had a total of 50 lesions at follow-up on the back and the right leg that would be classified as PD. Also, if a participant had no lesions at entry on the right arm and had five lesions on the right arm at follow-up that would be classified as PD. Similarly, if a participant had 40 lesions at entry and 20 lesions at weeks **9 and 15 (a confirmed PR)** but at a subsequent visit was found to have 30 lesions (a greater than 25% increase over the best response), the participant would have PD. **PD after a confirmed CR is defined by the presence of any KS following that confirmed CR.**

Please note that "best response" may improve after the initial **confirmed PR** is documented. For example, if the **entry** number of lesions was 30 and the number of lesions decreased to 15 at weeks **9 and 15**, this would be the initial **confirmed PR**. If, at the week 18 evaluation the number of lesions decreased further, e.g., to 10**, then 10 is the new "best response"** and subsequent assessments of PD for lesion counts would be with respect to the number 10, not to 15. **Furthermore, if the number of lesions at week 24 increased from 10 to 15, this increase would constitute PD, despite the fact that 15 is 50% smaller than the entry lesion count.**

> *Note:* **If a confirmed PR has been achieved and subsequent evaluations do not meet criteria for PD or CR, this would continue to be evaluated as PR. In the example above, if the entry lesion count was 30 and the number of lesions decreased to 15 at weeks 9 and 15, then 15 is the "best response" to date. If, at week 24, the number of lesions increased to 18, this would continue to be reported as a PR because 18 is less than a 25% increase from 15. Similarly, if at week 24, the number of lesions decreased by an additional 20% to 12, this would also continue to be reported as a PR.**

2.3 Calculate Response Status Based on the Total Number of Raised Lesions

To calculate the response status based on the number of raised lesions, you will need the total number of raised **lesions** (either whole body or, in the case of participants with >50 lesions at entry, in the combined representative areas) from the entry KS exam. If, after an initial **confirmed** response, the disease appears to be getting worse, the percentage change **for PD** should be calculated from the "best response" seen at a previous visit.

An initial confirmed PR is a complete flattening of at least 50% of all previously raised lesions (i.e., 50% of all nodular or plaque-like lesion become macules) present at entry (either whole body or, in the case of participants with >50 lesions at entry, in the combined representative areas) lasting for at least 4 weeks. For example, if a participant had 30 raised lesions at entry and had only 15 raised lesions at follow-up and this decrease was maintained for at least 4 weeks that would be classified as a **confirmed PR.**

For participants with ≤50 cutaneous lesions **at entry**, PD is defined as ≥25% increase in the

number of raised lesions (minimum of 5 new raised lesions if there are very few raised lesions, for example <8), compared to entry or best response. For example, if a participant had 20 raised lesions at entry and had 25 raised lesions at follow-up that would be classified as PD. Also, if a participant had 7 raised lesions at entry and had 12 at follow-up that would be classified as PD. **PD after a confirmed CR is defined by the presence of any KS following that confirmed CR.**

> *Note:* **If a confirmed CR has been achieved and subsequent evaluations do not meet criteria for CR, this would be reported as PD.**

For participants with >50 cutaneous lesions **at entry**, PD is defined as ≥25% increase in the total number of raised lesions **or a minimum of five new raised lesions, whichever is greater,** in the combined prospectively-defined anatomic sites containing representative lesions (minimum of 5 raised lesions if there are very few raised lesions, for example <8). For example, if a participant had a total of 28 raised lesions on the back and right arm at entry and had a total of 35 raised lesions on the back and right arm at follow-up that would be classified as PD. Also, if a participant had a total of 7 raised lesions on the back and right arm at entry and had 12 raised lesions on the back and right arm at follow-up that would be classified as PD. Similarly, if a participant had 40 raised lesions at entry and 20 raised lesions at weeks **9 and 15 (a confirmed PR)** but at a subsequent visit was found have 30 raised lesions (a greater than 25% increase over the best response), the participant would have PD. **PD after a confirmed CR is defined by the presence of any KS following that confirmed CR.**

Please note that "best response" may improve after the initial **confirmed PR** is documented. For example, if the **entry** number of raised lesions was 30 and the number of raised lesions decreased to 15 at weeks **9 and 15,** this would be the <u>initial</u> **confirmed PR.** If, at the week 18 evaluation, the number of raised lesions decreased further, e.g., to 10, **then 10 is the new "best response" and** subsequent assessments of PD for raised lesions would be with respect to the number 10, not to 15. **Furthermore, if the number of raised lesions at week 24 increased from 10 to 15, this increase would constitute PD, despite the fact that 15 is 50% smaller than the entry raised lesion count.**

> *Note:* **If a confirmed PR has been achieved and subsequent evaluations do not meet criteria for PD or CR, this would continue to be evaluated as PR. In the example above, it the entry raised lesion count was 30 and the number of raised lesions decreased to 15 at weeks 9 and 15, then 15 is the "best response" to date. If, at week 24, the number of raised lesions increased to 18, this would continue to be reported as a PR because 18 is less than a 25% increase from 15. Similarly, if at week 24, the number of raised lesions decreased by an additional 20% to 12, this would also continue to be reported as a PR.**

2.4 Determining Response Status Combining Measurements of Lesion Size, Character, and Number and Visceral Disease and Edema

Participants who show the absence of any detectable residual disease, including tumor-associated edema, persisting for at least 4 weeks, will be classified as having CR. In some individuals, residual skin color changes may remain visible at one or more sites of lesions that were previously raised and/or red or violaceous. Suspected CR in those lesions refers only to residual macules (flat, non-palpable lesions) that are slightly darker than the surrounding normal skin. In the event such lesions are present in a participant otherwise believed to have a CR, biopsy of at least one such lesion is required to document the absence of malignant cells and to confirm CR. In the event that such a confirmatory biopsy is not performed and residual pigment persists, the response will be considered **PR.** In participants in whom all detectable cutaneous disease has resolved and in whom there are no visible pigmented macules as described above, a confirmatory skin biopsy is not required. In participants known to have had visceral disease, an attempt at restaging with appropriate endoscopic or radiographic procedures should be made.

Participants who do not meet the criteria for **CR, PR,** or **PD** will be classified as Stable.

The criteria for classifying participants as showing either **PR** or **PD** are shown in the tables below.

Partial Response

PR requires at least one of the highlighted criteria in the table below AND all of the categories shown on the same row, when compared to entry.

Note: If any of the criteria for PD have been met, even in the presence of a criterion for **PR,** it is considered PD.

Note: **PR** is always a comparison to entry even if there has been a prior **PR**.

Criteria for Classifying **PR**					
Total body or representative areas					
PR Category	**Marker lesion area**	**Number of lesions**	**Number of raised lesions**	**Visceral or Oral KS***	**Edema**
1	**Decrease ≥50%**	<25% Increase	<25% Increase	<25% Increase of measurable lesions without unequivocal worsening of non-measurable disease	No significant increase or new sites
2	<25% Increase	**Decrease ≥50%**	<25% Increase	<25% Increase of measurable lesions without unequivocal worsening of non-measurable disease	No significant increase or new sites

Criteria for Classifying **PR**					
Total body or representative areas					
PR Category	**Marker lesion area**	**Number of lesions**	**Number of raised lesions**	**Visceral or Oral KS***	**Edema**
3	<25% Increase	<25% Increase	**Decrease ≥50%**	<25% Increase of measurable lesions without unequivocal worsening of non-measurable disease	No significant increase or new sites
4	<25% Increase	<25% Increase	<25% Increase	**Decrease ≥50% of measurable lesions without unequivocal worsening of non-measurable disease or complete disappearance of non-measurable disease**	No significant increase or new sites

*Please note that there is no need to physically measure the visceral or oral KS.

Progressive Disease

Any of the following (increase refers to a change over entry visit or when compared to the best response). If there has been a previous confirmed CR or PR, subsequent assessments of PD should be made with comparison to the best response for the category (or categories) that previously led to the assessment of CR or PR; for the other categories, the comparison should be made to entry.

> ***Note:*** PD is a comparison to entry unless there has been a **confirmed** PR or CR in which case it is then a comparison to best response. Only PD is compared to best response.

Total body or representative areas				
Marker lesion area	Number of lesions	Number of raised lesions	Visceral or Oral KS	Edema
≥25% Increase	≥25% Increase	≥25% Increase	≥25% Increase or new sites or unequivocal worsening of non-measurable disease	Significant increase or new sites*

*Significant increase in edema or new sites compared to entry or best response** are defined as:

- an increase in non-pitting/woody edema in an upper or lower extremity associated with an increase in limb circumference of at least 3 cm from entry **or best response**, sustained for at least two consecutive evaluations, and measured at a fixed point on the extremity with respect to a bony landmark (e.g., 10 cm below the lower border of the patella); AND/OR,

- new appearance of non-pitting/woody edema in an extremity when none was previously present, sustained for at least two consecutive evaluations;

  AND/OR,

- new or worsening edema in a non-extremity site (e.g., periorbital, genital) that interferes with function and is sustained for at least two consecutive evaluations.

  **** If edema is present at entry and resolves completely (and this lasts for at least 4 weeks), this is considered a "best response" of edema. Otherwise, all evaluations of edema in a given step are with respect to the status at entry to that step.**

2.5 Assessment of Response Status During Steps 2, 3 and 4

At the time of Step 2, 3, or 4 entry, a different representative area, if preferable, may be chosen for determination of response status during Step 2, 3, or 4. Response status during Step 2, 3 or 4 will be determined by comparing Step 2, 3 or 4 visits to Step 2, 3, or 4 entry, respectively. If possible, the same marker lesion(s) should be followed and measured throughout Steps 1, 2, 3, and 4.

3. Photographic Record

Photographs will be taken to assist in documentation of the diagnosis of KS and for clinical monitoring purposes. The difficulty in standardizing these photographs is acknowledged.

In all participants, photographs will be needed of the marker lesion(s), defined at study enrollment and used for clinical assessment of response. The marker lesion**(s)** must be labeled in the photographs #1–#5, **as applicable**. The same lesion**(s)** must be consistently labeled throughout the trial. For each lesion, two photos will be taken. The first photo will be a close-up of the lesion. A millimeter ruler should be included in the photograph to demonstrate the size of the lesion. The second photo will be a larger view photo that will show the lesion's location on the body.

In all participants, photos will also be needed of larger views of the back, chest, arms (front and back), legs (front and back), feet (including soles), whether involved with KS or not. In addition, photos should be taken of any other area with significant involvement at entry (e.g., the face).

In participants with >50 cutaneous lesions, photographs will be taken of the representative areas (each **should have at least 5** lesions), defined at study enrollment and used for clinical assessment of response.

Photographic documentation will be completed at entry and then at each visit when the KS response status changes. For example, if a participant's KS response status changes from no

response to **PR**, the site will take photos of this to document the category change. If there was no change in the KS response status, no photos are required.

> ***Note:*** The same markers lesions should be used throughout the study. In the event that the marker lesions coalescence or become immeasurable during follow-up, a new marker lesion may be selected at the entry of a new step for follow-up evaluations during that step.

Photographs will be stored electronically under the participant ID number and back-up electronic storage will be kept. Only dedicated study staff and the sponsor should have access to the photographs.

Appropriate measures must be taken to protect participant confidentiality. Photographs of participants' faces should be avoided unless the area is being monitored for KS response. In cases where a participant's face is photographed, no participant photos should be used in publication prior to removal of identifying characteristics, for example, the blacking out of a participant's eyes. **Site should take necessary measures to black out eyes and/or tattoos prior to uploading photos.**

Absolutely no identifying information should be included with the digital picture file.

Photography Tips

1. We recommend a 5 megapixel camera minimum.
2. Include the participants PID in all of the photos.
3. Always try to take the photos in the same setting with respect to participant positioning, lighting, background, and camera setting.
4. Use auto-focus. The team does not recommend the use of manual controls.
5. Use the "macro" mode for close-ups. The universal symbol for "macro" mode is a flower.
6. Use the flash mode as often as possible when the lighting is poor, but avoid getting too close to the lesions as overexposure may wipe out the details.
7. For very close shots, oblique views may be preferred
8. Eliminate all distractions from the background. Try to take all photographs with a plain blue or green background.

Framing Tips

1. For different body areas certain standard framing patterns are followed
2. For all lesions, make it a point to take at least 2 shots from each point of focus. Minimal blurring may not be obvious on the LCD screen and may be noticeable only after the image is viewed on the monitor. It is always better to have an extra copy from every focus point so that the best image can be selected.
3. Always try to capture distinctive elements like typical representative lesions, particular configurations, or distribution patterns.

For generalized lesions take shots from at least three ranges:

- A complete vertical view of the participant showing the extent and distribution of the rash;
- A medium distance shot showing the arrangement and configuration of the rash;

- A close-up view highlighting a representative lesion.

For localized lesions take shots from at least two points:

- A medium view showing the rash /lesion with respect to location and configuration

Always include a recognizable body landmark so that the location is obvious. For example, lesions on the abdomen include the umbilicus in the medium distance shot)

- A close-up view of the representative lesion

  For isolated lesions it is also advisable to include a discernible landmark in one of the shots. For the close-up shots use a measuring tape/ruler in the frame to demonstrate the size of the lesion. It would be advisable to take the close-up shots from more than one angle and include oblique shots. Shots with and without flash may be taken and the best shot selected for storage.

Recommended Saving, Storing, and Uploading Files

1. SAVE as a JPG file. The major advantage of the JPG format is that the image size can be compressed considerably without significant visible loss of resolution. The back-up copies can also be saved in the compressed JPG format so that the space taken up can be minimized. It always makes sense to delete images that are blurred as they are unlikely to be used by you and will unnecessarily clutter up the hard disk space.
2. Make it a point to catalog all saved images (or containing folders) tagging them with the participant's identification number, date and even the provisional diagnosis, if possible. Meticulous cataloging may seem cumbersome at the beginning but make future retrieval of images very convenient.

APPENDIX E KAPOSI SARCOMA RESPONSE SHEET

CITN-17 KAPOSI SARCOMA MEASUREMENT AND RESPONSE SUMMARY

Initials		Date		Study		Cycle		Photos	
Baseline TIS		T: I: S:			REASON T1:				

MARKER LESIONS

LESION	COLOR, LOCATION	FLAT OR NODULAR	DIMENSIONS	PRODUCT
ONE				
TWO				
THREE				
FOUR				
FIVE				

LESION COUNT

TOTAL LESIONS	OVER 50 _____ UNDER 50* _____
*FOR PATIENTS WITH UNDER 50 LESIONS, WRITE 'TOTAL BODY' FOR AREA AND USE LEFT COLUMN	

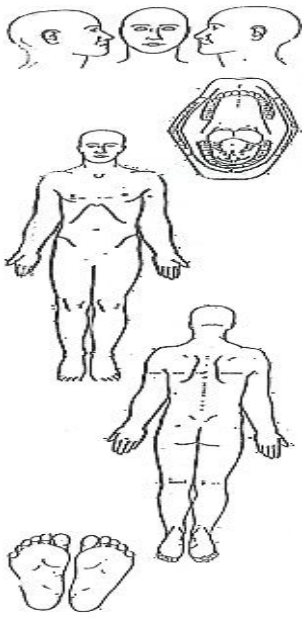
BODY AREA	1	2	3	TOTAL
NUMBER FLAT				
NUMBER NODULAR				
TOTALS				

ORAL LESIONS	PRESENT		NONE		NO EVAL	
DESCRIPTION IF PRESENT						
VISCERAL LESIONS	PRESENT		NONE		NO EVAL	
DESCRIPTION IF PRESENT						

RESPONSE THRESHOLDS FROM:_____				RESPONSE FROM BASELINE	
PARTIAL RESPONSE		PROGRESSIVE DISEASE		RESPONSE BASED ON	
TOTAL		TOTAL		RESPONSE FROM BEST RESPONSE	
NODULAR		NODULAR		RESPONSE BASED ON	
PRODUCT		PRODUCT		RESPONSE CONFIRMED BY	
RECORDER				SIGNATURE	

TUMOR EDEMA
NO [ ] YES [ ] LOCATION

LEFT			RIGHT		
LEVEL	DIST.	DIAM.	LEVEL	DIST.	DIAM.
ANKLE	0cm		ANKLE	0cm	
CALF			CALF		
THIGH			THIGH		
PELVIS			PELVIS		



APPENDIX F PATIENT CLINICAL TRIAL WALLET CARD

NIH NATIONAL CANCER INSTITUTE

CLINICAL TRIAL WALLET CARD

Show this card to all of your healthcare providers and keep it with you in case you go to the emergency room.

Patient Name:
Diagnosis:
Study Doctor:
Study Doctor Phone #:
NCI Trial #:
Study Drug(S):

For more information: 1-800-4-CANCER

cancer.gov | clinicaltrials.gov