TITLE: PEDIATRIC AND YOUNG ADULT LEUKEMIA ADOPTIVE THERAPY (PLAT)-07: A PHASE 1/2 STUDY OF CD22-SPECIFIC CAR T CELLS FOR CD22+ LEUKEMIA OR LYMPHOMA

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Indication:	Refractory or recurrent CD22+ leukemia or lymphoma
IND Number:	22973
Sponsor:	Seattle Children's, Seattle Children's Therapeutics 1920 Terry Ave Seattle, WA 98101
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This study is to be performed in compliance with the protocol, Good Clinical Practices (GCP) and applicable regulatory requirements.

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1 LIST OF ACRONYMS, ABBREVIATIONS, AND DEFINTION OF TERMS

ACD	Acid-citrate-dextrose
ADA	Adenosine deaminase
AE	Adverse event
ALC	Absolute lymphocyte count
ALL	Acute lymphoblastic leukemia
Allo-HCT	Allogeneic hematopoietic cell transplant
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
BCA	B cell aplasia
BiTE	Bispecific T cell engaging
BM	Bone marrow
BUN	Blood urea nitrogen
CAPD	Cornell Assessment of Pediatric Delirium
CAR	Chimeric antigen receptor
CBC	Complete blood count
CFR	Code of Federal Regulations
CLL	Chronic lymphocytic leukemia
CMV	Cytomegalovirus
CNS	Central nervous system
COG	Children's Oncology Group
CR	Complete response / Complete remission
CRF	Case Report Form
CRS	Cytokine release syndrome
CSF	Cerebrospinal fluid
CSL	Correlative studies laboratory
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
CTL	Cytotoxic T lymphocyte
CXR	Chest x-ray
DFS	Disease-free survival

DLI	Donor lymphocyte infusion
DLT	Dose limiting toxicity
DMC	Data Monitoring Committee
EBV	Epstein-Barr virus
ECHO	Echocardiogram
DMSO	Dimethyl sulfoxide
EFS	Event free survival
EGFR	Epidermal growth factor
FDA	Food and Drug Administration
g	gram
GCP	Good Clinical Practice
GVHD	Graft versus host disease
GVL	Graft versus leukemia
h	hour
HCT	Hematopoietic cell transplant
HER2	Human epidermal growth factor receptor 2
HIPAA	Health Insurance Portability and Accountability Act
HLA	Human Leukocyte antigen
IB	Investigator's Brochure
IBC	Institutional Biosafety Committee
ICANS	Immune effector Cell-Associated Neurotoxicity Syndrome
ICE	Immune effector Cell-Associated Encephalopathy
ICF	Informed consent form
IEC	Institutional Ethics Committee
IFNγ	Interferon type II gamma
IL	Interleukin
IND	Investigational New Drug (application)
IRB	Institutional Review Board
ITAMs	Immunoreceptor tyrosine activation motifs
IV	Intravenous
L	Liter
LDH	Lactate dehydrogenase
LP	Lumbar puncture
LTFU	Long-term follow-up
m^2	meters squared

MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
MHC	Major histocompatibility complex
mL	milliliter
mm^3	millimeter
MPF	Multiparameter flow cytometry
MRCL	Minimal response cytolytic
MRD	Minimal residual disease
MRD-negative CR	Minimal residual disease negative Complete Remission
MRD-positive CR	Minimal residual disease positive Complete Remission
MRD-negative CRi	Minimal residual disease negative Complete Remission without count recovery
MRD-positive CRi	Minimal residual disease positive Complete Remission without count recovery
MRI	Magnetic resonance imaging
MSKCC	Memorial Sloan-Kettering Cancer Center
MTD	Maximally tolerated dose
NCI	National Cancer Institute
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NIH	National Institutes of Health
NHL	Non-Hodgkin lymphoma
NRM	Non-relapse mortality
OS	Overall survival
PCR	Polymerase chain reaction
PBMC	Peripheral blood mononuclear cell
PD	Progressive disease
PET	Positron emission tomography
PI	Principle Investigator
PLAT	Pediatric Leukemia and lymphoma Adoptive Therapy
PJP	Pneumocystis jiroveci pneumonia
PR	Partial response / Partial remission
PRCL	Partial remission cytolytic
RCL	Replication-competent lentivirus

rhuIL-2	Recombinant Human Interleukin-2
SAE	Serious adverse event
scFv	single chain variable fragment
SCID	Severe combined immunodeficiency
SCRI	Seattle Children's Research Institute
SCTx	Seattle Children's Therapeutics
SD	Stable disease
SIN	Self-inactivating
SITE	Study Implementation Team
SOP	Standard operating procedure
SPRT	Statistical Proabability Ratio Test
TCPC	Therapeutic cell production core
TBI	Total body irradiation
TCM	Central memory T cell
TCR	T cell receptor
TE	Effector T cell
Treg	Regulatory T cell
TIL	Tumor infiltrating lymphocyte
TKI	Tyrosine kinase inhibitor
ULN	Upper limit of normal
WBC	White blood cell

Definition of Terms
Investigational Product is defined as, "A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use" (from International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use [ICH] Harmonized Tripartite Guideline E6: Guideline for Good Clinical Practice.
The terms "Investigational Product" and "study drug" may be used interchangeably in the protocol.

2 ABSTRACT

This phase 1/2, open-label, non-randomized study will enroll pediatric and young adult patients with relapsed or refractory $CD22^+$ leukemia or lymphoma with and without prior history of allogeneic hematopoietic cell transplantation, to examine the safety, feasibility, and efficacy of administering T cell products derived from autologous peripheral blood mononuclear cells (PBMC) that have been genetically modified using a self-inactivating SIN lentiviral vector to express a CD22-specific chimeric antigen receptor (CAR), and the selection-suicide marker EGFRt (SCRI-CAR22v2).

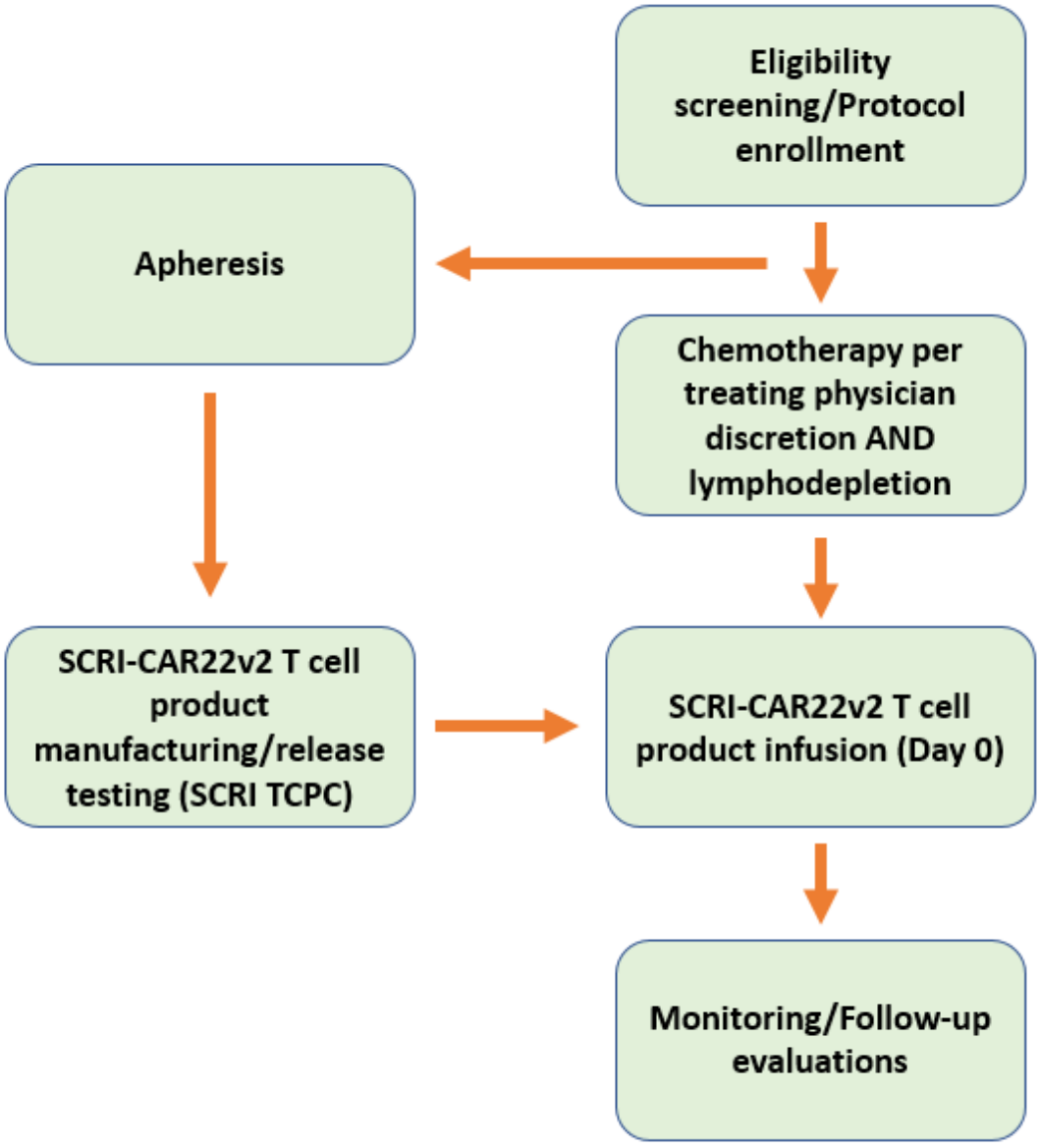
Subjects will receive a single dose of T cells. CD4 and CD8 T cell subsets will be isolated from apheresis product obtained from the research subject. The isolated cells will be stimulated with anti-CD3 x anti-CD28 beads and transduced with a SIN lentiviral vector that directs the co-expression of the CD22-8a-41BBz CAR and EGFRt. Modified cells will be propagated using recombinant human cytokines to numbers suitable for clinical use. The product will be cryopreserved and release testing performed. Once the patient has recovered from any acute toxicities from re-induction/salvage chemotherapy, the SCRI-CAR22v2 will be infused via an indwelling catheter.

The Phase 1 portion of the study is based on a 3+3 design with three possible dose levels to explore. During the Phase 2 portion, a two-stage statistical design will be employed to minimize the maximum number of subjects treated, and in which the study will stop in futility if minimal response rates are not met. In addition to efficacy, a safety monitoring rule will assess toxicity during Phase 2, with the initial review occurring after treatment of the initial 12 subjects. The primary objectives of the study will be to determine the feasibility of manufacturing the cell product as well as to assess the safety of the SCRI-CAR22v2 including a description of the full toxicity profile. The maximum tolerated dose (MTD) will be determined using a 3+3 design, cohorts of 3 subjects, with 3 dose levels to explore. Additionally, a biologically effective dose (BED) may be determined prior to the MTD based on efficacy and *in vivo* persistence of SCRI-CAR22v2. Cohort advancement will take place after all patients of the current cohort have been evaluated for dose limiting toxicities.

The secondary objectives of this protocol are to study the engraftment and *in vivo* persistence of SCRI-CAR22v2 in the peripheral blood, bone marrow and CSF as well as to describe efficacy and toxicity in the leukemia and lymphoma subjects separately. Subjects who experience significant and potentially life-threatening toxicities (other than clinically manageable cytokine release syndrome or neurotoxicity) will receive infusions of cetuximab to assess the ability of the EGFRt transgene to be an effective suicide mechanism for the ablation of transferred T cell products.

2.1 Trial Schema

2.1.1 Experimental Design Schema



3 BACKGROUND/RATIONALE

3.1 Relapsed/Refractory Acute Leukemia and Non-Hodgkin Lymphoma

Acute Lymphoblastic Leukemia (ALL) is the single most common type of cancer afflicting children with a high overall cure rate of >80%. The upfront treatment for childhood ALL involves a prolonged course of multidrug chemotherapy that is dose and time intensive and is augmented for subjects identified as high risk[1,2]. While event free survival (EFS) and overall survival (OS) have greatly improved for newly diagnosed subjects with ALL, those who relapse after intensive upfront therapy often have chemo-resistant disease[3,4], with OS rates of only 40-50%[2,5,6]. Additionally, subjects who relapse a second or greater time have decreasing rates of responsiveness to chemotherapy, with declining rates of complete response (CR); 44% with 3rd treatment, and 27% with 4th treatment) and an OS of <20%[5]. The best therapeutic option capable of achieving disease eradication for children with relapsed ALL often includes an allogeneic hematopoietic cell transplantation (allo-HCT), provided a suitable donor is available and the disease is controlled prior to transplant[3,7,8].

The presence of minimal residual disease (MRD), as defined by greater than 0.01%, at the time of allo-HCT, is a significant predictor of post-HCT relapse and poor OS[9]. On the Children's Oncology Group (COG) relapsed ALL study AALL01P2, 62% of patients remained MRD positive at the end of block 1 of reinduction, and their 3-year EFS rate was 24%[6]. Thus, the development of therapeutic strategies with augmented anti-ALL activity is warranted to increase the percentage of patients who achieve an MRD negative remission prior to allo-HCT, which in turn would be expected to increase the proportion of patients who are ultimately cured.

Relapse of ALL following allo-HCT is often not responsive to further chemotherapy and survival is dismal. Treatment strategies for relapse following allo-HCT include weaning of immunosuppression to invoke a graft versus leukemia (GVL) response, and if feasible, the use of donor lymphocyte infusion (DLI). Unfortunately, ALL is amongst the least responsive hematologic malignancies to a GVL effect, demonstrated by frequent occurrence of relapse despite graft versus host disease (GVHD) and low response rate to DLI[10,11]. Therefore, alternative treatment strategies are also needed for relapsed ALL post allo-HCT.

Non-Hodgkin lymphoma (NHL) is the fourth most common pediatric malignancy, with overall survival rates now exceeding 80%. The upfront treatment for NHL involves dose intensive chemotherapy for nearly all patients, requiring frequent hospitalizations and prolonged periods of neutropenia with risk of infection. Furthermore, outcomes for relapsed NHL are dismal, with cure rates of less than 30% despite reinduction treatment regimens using high dose chemotherapy often followed by consolidative HCT[12-14], highlighting a need for additional therapies in this population.

The vast majority of pediatric NHL is high grade lymphoma, mostly of B cell origin[15]. The anti-CD20 antibody rituximab is now often standardly incorporated into upfront and relapsed therapy regimens for cohorts of adult and pediatric mature B cell NHL. Promising newer immunotherapy agents in adult mature B cell NHL include alternative monoclonal antibodies, such as the next-generation CD20 targeting antibody obinutuzumab[16] and the Bruton-tyrosine kinase antibody ibrutinib[17], although these have not been investigated to date in childhood B cell NHL. Since both pre-B and mature B cell NHL tend to express CD22, immunotherapies that target CD22 represent another intriguing approach, such as inotuzumab and CD22 targeting chimeric antibody receptor (CAR) T cell therapy.

3.2 CAR T Cell Background

We have focused on T cell genetic engineering strategies that serve to equip T cells with tumor specificity through the expression of CARs[18]. CARs are engineered to consist of an extracellular single chain antibody fused to the intracellular signaling domain of the T cell antigen receptor complex zeta chain, and when expressed in T cells, are able to redirect antigen recognition based on the monoclonal antibody's specificity[19]. These chimeric cell-surface molecules have the ability to bind antigen and transduce activation signals via immunoreceptor tyrosine activation motifs (ITAMs) present in the CD3-ζ cytoplasmic tail[20], or both activation and co-stimulatory signals when CD28 and/or 4-1BB/OX40 domains are incorporated in series with CD3-ζ[21,22].

The design of scFvFc:ζ receptors with target specificities for tumor cell-surface epitopes is a conceptually attractive strategy to generate antitumor immune effector cells for adoptive therapy as it does not rely on pre-existing anti-tumor immunity. These receptors are "universal" in that they bind antigen in a MHC-independent fashion, thus, one receptor construct can be used to treat a population of patients with antigen positive tumors. Several constructs for targeting human tumors have been described in the literature, including receptors with specificities for HER2/Neu, CEA, ErbB-2, CD44v6, and epitopes selectively expressed on renal cell carcinoma[23-27]. These epitopes all share the common characteristic of being cell-surface moieties accessible to scFv binding by the chimeric T cell receptor. The function of primary human T cells expressing tumor-specific scFvFc:ζ receptors have been evaluated *in vitro*; these cells specifically lyse tumor targets and secrete an array of pro-inflammatory cytokines including IL-2, TNF-α, IFN-γ, and GM-CSF[28].

Adoptively transferred CAR T cells can eradicate established tumors in a variety of animal models[29-35]. Moreover, T cells expressing second or third generation CARs consisting of co-stimulatory signaling domains appear to be more resistant to activation induced cell death, exhaustion, and T_{REG}-mediated functional anergy[21,22,29,36-41]. There is no conclusive data regarding which co-stimulatory signaling domain is superior. Previous studies have shown that CD28 significantly increases IL-2 production but 4-1BB seems to improve survival of the T cells. Both signaling domains, CD28-CD3-ζ and 4-1BB-CD3-ζ, are used in clinical

trials targeting CD19. Our local investigations through Seattle Children's Research Institute (SCRI) have utilized 4-1BB-CD3-ζ signaling domain.

3.3 CD22 as an immunotherapy target

Efforts to target hematologic malignancies with CAR-modified T cells have focused predominantly on cell lineage specific molecules. Normal and malignant B cells express surface molecules that define their lineage commitment and maturation stage, and several are being investigated as targets for antibody or cellular therapy. These include CD20, which is present on B cell lymphomas and CLL, and has been targeted effectively with rituximab [42-44]. However, CD20 is expressed late in B cell development and is often not present on ALL [45]. By contrast, CD22 is expressed on all human B cells beginning from the pre-B cell phase, and is present on the majority of adult and pediatric ALL and B cell lymphomas [46].

CD19 CAR T cells have demonstrated significant success in targeting $CD19^+$ ALL and lymphoma in patients previously refractory to standard, intensive chemotherapy. Our experience has demonstrated a greater than 90% complete remission rate following CD19 CAR T cells in B-ALL. However, this response is sustained in only half of patients. Lack of sustained remission is due to a number of issues including CD19 antigen negative relapse [47]. Studies have demonstrated CD19 epitope modification following CD19 targeted therapy converts the epitope to an unrecognizable antigen target [48]. Thus, for therapy of B-ALL and B cell lymphoma, we have constructed a CD22-specific CAR.

A multi-center randomized trial was recently published discussing the results of a Phase 3 trial evaluating the efficacy of inotuzumab ozogamicin (CMC-544), an anti-CD22 antibody conjugated to calicheamicin, a cytotoxic agent, as compared to intensive standard chemotherapy in adults with relapsed or refractory CD22+ ALL. Those that received inotuzumab ozogamicin had a higher complete remission rate (80.7%) where only 29.4% of the standard therapy cohort achieved a CR ($p<0.0001$). The duration of remission was prolonged in the inotuzumab ozogamicin cohort as well with a median time to progression was 4.9 months as compared to 3.1 months on the standard therapy arm ($p = 0.03$). The most frequent Grade 3 or higher non-hematologic adverse events with the CD22 targeted therapy were liver-related, including veno-occlusive disease in 11% of patients.[49] This is also seen with Mylotarg and likely related the calicheamicin component of the therapy as this has not been observed in our CD19 CAR trial.[50] This study suggests targeting CD22 is potentially an additional efficacious target to improve ALL remission rates.

The National Institute of Health and National Cancer Institute opened a CD22 CAR T cell trial for pediatric and young adult patients in 2014. Twenty-one patients have been treated, ages 7-30 years. All had previously been diagnosed with CD22+ ALL. Of those, 17 had previously received CD19 targeted therapy and developed a CD19 negative or dim relapse. Patients received transduced cell doses ranging from $3x10^5$/kg to $1x10^6$/kg. Sixteen patients

experienced CRS, with onset after Day +5 in all patients. Grade 1 CRS occurred in 9 patients, Grade 2 in 7 patients. One experienced Grade 3 diarrhea during CRS which resolved with supportive care but results in a dose limiting toxicity at the first dose level. Two patients that received Dose Level 3 and one developed dose limiting hypoxia (Grade 4) which resolved following steroid treatment. Among the first 16 patients with full assessment described, 2 developed visual hallucinations, one with mild unresponsiveness, one with mild disorientation and two with mild-moderate pain. All returned to baseline 4 weeks following infusion.[51] Following this initial study report a manufacturing change was implemented which incorporated CD4 and CD8 T cell selection from the apheresis product for manufacturing[52] (a procedure also used in the manufacturing of SCRI-CAR19v2). With this new manufacturing step a new toxicity profile was observed. A majority (86%) of subjects developed grade 1-2 CRS. Two subjects experienced a grade 5 event at dose level 2 ($1x10^6$ cells/kg), one with bacteremia, sepsis and organ dysfunction. The second subject experienced capillary leak syndrome during CRS leading to pulmonary dysfunction. Additionally, at dose level 2 there was an increased number of subjects with hemophagocytic lymphohistocytosis (HLH)/macrophage activation syndrome (MAS) (5 of 7 subjects treated) and therefore dose reduction (to dose level 1, $3x10^5$ cells/kg) took place with a subsequent reduced incidence of HLH/MAS from 71% to 44% of subjects. Forty percent of subjects that developed CRS also developed HLH/MAS clinical findings, 2 weeks from T cell infusion on average with preceding resolution or near resolution of CRS. In 5 subjects HLH/MAS resolved without intervention. Fourteen subjects received anakinra and/or corticosteroids to treat the CD22 CAR T cell induced HLH/MAS. All subjects had resolution of HLH/MAS without an apparent impact on T cell expansion or disease response. Additionally, a third of subjects experienced a neurologic abnormality, grade 1 or 2, following receipt of the immunotherapy. One subject did develop an intracranial hemorrhage at dose level 1 ($3x10^5$/kg), felt to be related to the T cell therapy and infection. Neurotoxicity events were limited per report or resolved by 4 weeks post infusion. Regarding disease response, of the 57 subjects treated, approximately 60% achieved a MRD negative complete response and an additional 10% achieved a complete morphologic response[52]. The reported experience from the NIH/NCI suggest CD22 is a viable target and CD22 CAR T cell therapy is potentially an efficacious approach with an acceptable toxicity profile.

3.4 Rationale for Lymphodepletion

The size of the T cell pool is subject to homeostatic regulation, and the induction of lymphopenia results in the proliferation of residual T cells to restore T cell numbers[53-55]. The lymphopenic environment may be more favorable for T cell transfer because of less competition for homeostatic cytokines such as IL-15 and IL-7 that promote lymphocyte proliferation and survival[56-58], and the elimination of CD4+ CD25+ regulatory T cells[59,60]. Direct evidence that the induction of lymphopenia improves the persistence of transferred tumor-reactive T cells was provided by studies at the NCI in which melanoma patients were treated with fludarabine and cyclophosphamide to induce lymphopenia prior to the transfer of 10^{10}-10^{11} polyclonal melanoma-specific T cells. A subset of these patients achieved

prolonged high-level engraftment of a few clonotypes in the transferred T cell population, and this correlated with antitumor efficacy[61,62]. Studies in murine models confirmed the human data that lymphodepletion can be exploited to improve the antitumor efficacy of transferred T effector (TE) cells, and provided evidence that hematopoietic stem cell (HSC) infusion further promoted the antitumor activity of T cell transfer[63,64]. Lastly, our Institution's CD19 CAR trial (PLAT-02) data suggests increased modified T cell activity demonstrated by persistent B cell aplasia (absence of CD19 expressing cells) following receipt of fludarabine and cyclophosphamide as compared to cyclophosphamide alone. Approximately 20% of patients that received cyclophosphamide alone continued to demonstrate B cell aplasia at 12 months following T cell infusion compared to 35% of patients who received fludarabine and cyclophosphamide. Studies in adults with NHL and ALL also had improved persistence of transferred CAR T cells with the addition of fludarabine to cyclophosphamide[65,66]. These data suggest lymphodepletion prior to adoptive transfer is an important factor in modified cell persistence, and specific lymphodepletion regimens can enhance persistence.

3.5 CAR T Cell Therapy Experience with SCRI investigational products

For Seattle Children's Hospital study PLAT-02, we developed a CAR consisting of tumor targeting, murine-based single-chain variable fragments (scFvs) specific for CD19[18,67-72]. Based on the V_H and V_L sequences of the CD19-specific murine IgG1 monoclonal antibody FMC63 published by Nicholson et al, an scFv sequence was constructed *de novo* utilizing PCR[73]. A full length CD19scFvIgG4hinge:CD28tm/41BB was constructed by PCR splice overlap extension and consists of the human GM-CSF receptor alpha chain leader peptide, FMC63 V_L, Gly-Ser linker, FMC63 V_H, human IgG_4 hinge, human CD28 transmembrane domain, 4-1BB intracellular cytoplasmic domain (residues 191-232) and CD3ζ (residues 31-142). Further, a truncated human EGFR selection/tracking/suicide construct is co-expressed with the CAR in constructs designed with T2A cleavable linkers[74]. When incorporated into third generation SIN lentiviral vectors, transduced T cells exhibit CD19-specific tumor cell recognition, lysis, cytokine secretion and proliferation[75].

The surface expression of EGFRt in conjunction with the CAR provides for a second cell surface marker that allows easy examination of transduction efficiency. Biotinylated Erbitux binds to the EGFRt expressed on the cell surface and can be labeled with fluorochrome for analysis with flow cytometry. Additionally, it can be used for enrichment through selection with anti-biotin beads to increase the frequency of transduced cells and thus creating a purified population of CAR-expressing T cells. Because the EGFRt lacks an intracellular domain, it does not have any signaling capacity, thus binding of Erbitux to the EGFRt does not affect the cell. Lastly, it has the potential to be used as a suicide gene in the clinical setting with the treatment of Erbitux, a clinically available antibody with a low toxicity profile. After binding of Erbitux, cells undergo antibody-dependent cellular cytotoxicity *in vivo*. Erbitux therefore is an available strategy on PLAT-02 in which CAR T cells could be

ablated if they are no longer required for efficacy, or alternatively, could be used in conjunction with glucocorticoids for ablation of T cells due to toxicity.

3.5.1 Clinical results from PLAT-02 – Phase 1

Results from the Phase 1 portion of PLAT-02 are available in which 45 subjects were enrolled and 43 treated from Dose Level 1 ($5x10^5$ CAR T cells/kg) through Dose Level 4 ($10x10^6$ CAR-T cells/kg)[50]. T cell products were released on all 45 enrolled subjects, with one subject requiring a second apheresis. Two subjects died of disease prior to their infusion. All 43 infused subjects received lymphodepletion chemotherapy prior to T cell infusion. T cell infusions were well tolerated with only one related AE greater than Grade 2. Ninety-three percent (40/43) of subjects had a documented MRD-negative CR within 21 days following CAR T cell therapy. The 12-month event-free survival (EFS) is 50.8% and 12 month OS is 69.5%.

All responding subjects exhibited *in vivo* expansion of CAR-T cells. The percent of CAR T cell expansion over time was found to be impacted by disease burden and total CD19 antigen burden at the time of lymphodepletion, rather than T cell dose. The median duration of functional CAR T cell persistence as measured by ongoing B cell aplasia (BCA) was found to be impacted by the total CD19 antigen burden in the bone marrow at time of lymphodepletion (>15% vs <15%), with a median of 6.4 months vs 1.7 months, respectively. Eighteen patients developed ALL relapse following T cell therapy. Seven were CD19 negative. Any grade CRS was seen in 93% of infused subjects with severe CRS in 23%. Any grade neurotoxicity was seen in 49% with a rate of severe neurotoxicity of 21%. Severity of CRS felt to be related to dose level and not disease burden, total CD19 antigen burden or lymphodepletion regimen. There were no toxic deaths on the Phase 1 portion of the trial[50].

3.5.2 Barriers to the Clinical Success of CD19 CAR T Cell Therapy

As reviewed above, CD19 CAR T cells have demonstrated significant success in targeting CD19+ ALL in patients previously refractory to standard, intensive chemotherapy. However, this response has been sustained in only half of patients. Lack of sustained remission is due to a number of issues including CD19 antigen negative relapse[50]. Studies have demonstrated CD19 epitope modification following CD19 targeted therapy converts the epitope to an unrecognizable antigen target[48]. This antigen escape is the cause of a lack of sustained remission in close to 25% of treated subject and indicates a need to target additional antigens such as CD22, which is being explored in other ongoing studies. Early loss of persistence of CD19-specific CAR T cells has also been shown to increase the risk of CD19+ relapse, and additional efforts have focused on enhancing persistence. Although the use of 4-1BB co-stimulation does appear to promote persistence, long term persistence is not uniformly seen. One explanation for short persistence is an immune-mediated rejection of the CAR construct, typically aimed at the murine-based scFv domain[65]. Therefore, more recent efforts have focused on the use of humanized or fully human CAR constructs as well as the development of additional targets of the CAR.

3.6 Development of SCRI-CAR22

3.6.1 Development and evaluation of SCRI-CAR22v1

The first trial of CAR T cells targeting CD22 at SCRI was PLAT-04, which opened in 2017 and 4 subjects were treated on the trial. SCRI-CAR22v1 was a CAR T cell product with CD22scRvIgG4hinge-CH2(L235D)-CDH3-CD28tm/4-1BBζ-T2A-EGFRt CAR. The first 3 subjects received the first cell dose at $1x10^6$/kg transduced CAR T cells and the 4th subject received $3x10^6$/kg CAR T cells. Products were successfully produced for all subjects and released for infusion. The first subject achieved an MRD negative remission as determined by bone marrow evaluation at Day 21. Prior to T cell infusion the subject's bone marrow was negative for disease; however, the subject had multiple sites of extramedullary disease demonstrated by PET imaging scan. The subject's extramedularly disease remained present at disease assessment, 3 weeks from CD22 CAR infusion. The next 2 subjects entered the study with varying amounts of bone marrow CD22 leukemia which remained stable or progressed at Day 21 evaluation. Additionally, a 4th subject was infused at Dose Level 2 given the lack of a DLT in the first dose cohort. This subject tolerated the infusion without a DLT; however, also had no measurable disease response at Day 21 (Figure 3-1). All subjects pursued alternative disease targeting therapy. Three of four subjects have since relapsed and 2 have died of disease. The fourth subject received CD19 CAR T cells following SCRI-CAR22v1 and is still alive. Study enrollment was ended due to concern of lack of efficacy for SCRI-CAR22v1.

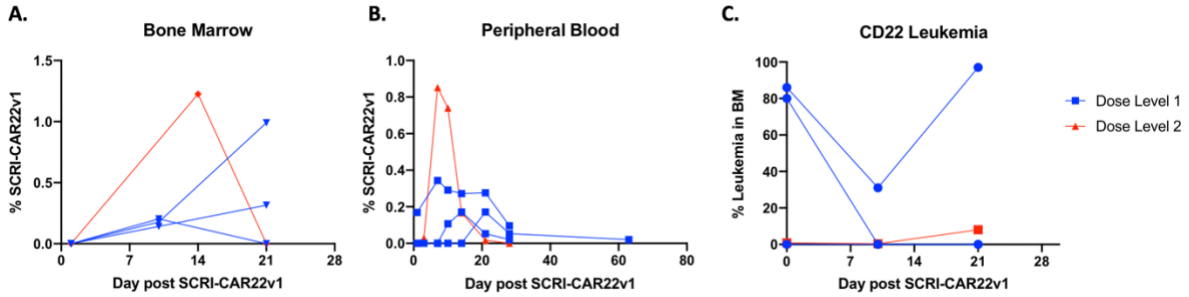


Figure 3-1. Results from PLAT-04 trial using SCRI-CAR22v1. A and B. There was some, though minimal, expansion noted in the bone marrow and peripheral blood compartments following SCRI-CAR22v1 infusion. C. The SCRI-CAR22v1 did not demonstrate CD22 leukemia control

3.6.2 Development of SCRI-CAR22v2

SCRI-CAR22v2 was assembled using the same CD22 scFV (m971791), 4-1BB costimulatory domain, and EGFRt extracellular domain (for transduction assessment and in vivo tracking). The transmembrane region incorporates CD8 alpha region, replacing IgG4 CH2-CH3 hinge and CD28 transmembrane region used in SCRI-CAR22v1. SCRI-CAR22v1 and v2 preliminary preclinical evaluations suggest the potential for early exhaustion in SCRI-CAR22v1 T cells following CD22 activation. Both versions of the CAR effectively target

CD22 antigen and demonstrate CD22 targeted cell lysis as demonstrated in chromium release assay (Figure 3-2:A) and CD22 targeted activation as demonstrated by cytokine production following CD22 exposure (Figure 3-2:B & C). Analysis quantifying IL2 production (Figure 3-2: B) demonstrated increased IL2 production from SCRI-CAR22v1 producing T cells, suggesting increased activation. An *in vivo* dose titration study using the Raji tumor model in NSG mice demonstrated improved tumor clearance at lower CAR T cell doses in the mice that received SCRI-CAR22v2, potentially demonstrating improved *in vivo* survival (Figure 3-2). These results suggest SCRI-CAR22v1 T cells' activation led to early exhaustion and may have been the cause of lack of efficacy seen in PLAT-04.

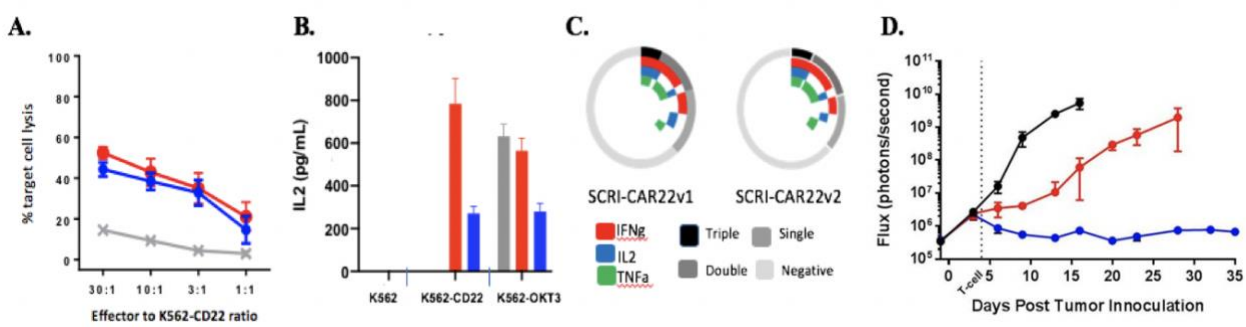


Figure 3-2 Comparison of SCRICAR22v1 and SCRI-CAR22v2.

A. SCRI-CAR22v1 (red) and SCRI-CAR22v2 (blue) were exposed to CD22 expressing target cells (K562 cells expressing CD22 antigen, K562-CD22) in a chromium release assay and both demonstrate CD22 targeted cell lysis.
B. Again cells were exposed to target cells (K562, K562-CD22 and K562-OKT3 (K562 cells expressing OKT3)) for 24 hours and IL2 production was measured. Both CARs secreted IL2 when stimulated via the CAR from CD22 exposure or endogenous T cell receptor (K562-OKT3). SCRI-CAR22v1 (red) secreted higher levels of IL2, as compared the SCRI-CAR22v2 (blue). Untransduced, mock T cells (gray) only secreted IL2 when exposed to K562-OKT3.
C. Intracellular cytokine production for IFNg, TNFa, and IL2 were measured following CD22 antigen expressing target cell exposure. Both CARs produce similar levels of cytokines.
D. NSG mice were infused with Raji tumor cells expressing ffluc for quantification and received 3x106 CD22 CAR T cells. SCRI-CAR22v2 (blue) treated mice demonstrated tumor control as demonstrated by measured flux as compared to SCRI-CAR22v1 (red). Both demonstrated improved control over control, mock T cells (black) as measured by flux.

3.7 Potential Toxicity Associated With SCRI-CAR22v2

This is a first-in-human study therefore the adverse effects of this product are not yet known. Similar studies of CAR T cells in B-ALL and NHL have seen the most common toxicity arising from cytokine release syndrome (CRS), and neurotoxocity. Other attributed adverse events seen less frequently include renal dysfunction, headaches, capillary leak, electrolyte distrubances, prolonged cytopenias and febrile neutropenia.

3.7.1 Cytokine Release Syndrome

It is commonly observed that patients receiving therapeutic T cells develop cytokine release syndrome (CRS) shortly following infusion of the product, with symptoms of fever, chills, rigor, mild hypotension and mild respiratory distress. Although these toxicities can occur immediately following the T cell infusion, they typically have an onset of 3-10 days after the T cell infusion and can last for up to 1-2 weeks.

Of the 43 patients treated on the Phase 1 portion of PLAT-02, 40 demonstrated CRS following their T cell infusion. Of those, 30 episodes were considered mild and did not require the use of vasopressors or inotropes. All CRS symptoms were fully reversible. The severity of CRS was related only to dose level and not to disease burden, CD19 antigen load, or lymphodepletion. Within the Phase 1 PLAT-02 cohort of patients, we evaluated the use of pre-emptive immune modulatory agents tociluzumab and dexamethasone. Comparing subjects who did and did not receive pre-emptive tociluzumab, with or without dexamethasone, the subjects who did not receive pre-emptive therapy demonstrated higher rates of severe CRS: 30% (7/23) versus 15% (3/20) for those who received early CRS targeted therapy. Early intervention with immunomodulation reduces severe CRS rates while preserving CAR T cell engraftment, persistence and remission rates[76].

Similar studies of CD19 CAR T cell therapy also report CRS with a range of severe CRS 14-25%[65,77-79]. There have been several pediatric and adult subjects treated on CD19 CAR T cell studies who developed Grade 5 CRS that was refractory to immunomodulatory interventions. During the initial experience of the NIH/NCI CD22 CAR T cell trial CRS was observed; however, only ranged from Grade 1 to 3 in severity with no Grade 5 events observed. Of the 21 patients currently described, 16 patients experienced CRS, with the onset occurring on or after Day +5 in all patients. Grade 1 CRS occurred in 9 patients and Grade 2 in 7 patients. One subject experienced Grade 3 diarrhea during CRS which resolved with supportive care but resulted in a dose limiting toxicity at the first dose level. Two patients received Dose Level 3 ($3x10^6$ CAR cells/kg) and one subject developed dose limiting hypoxia (Grade 4) which resolved following steroid treatment[51]. Following this initial study report a manufacturing change was implemented which incorporated CD4 and CD8 T cell selection from the apheresis product for manufacturing[52] (a procedure also used in the manufacturing of SCRI-CAR19v2). With this new manufacturing step a new toxicity profile was observed. A majority (86%) of subjects developed grade 1-2 CRS. Two subjects experienced a grade 5 event at dose level 2 ($1x10^6$ CAR cells/kg), one with bacteremia, sepsis and organ dysfunction. The second subject experienced capillary leak syndrome during CRS leading to pulmonary dysfunction. Additionally, at dose level 2 there was an increased number of subjects with hemophagocytic lymphohistocytosis (HLH)/macrophage activation syndrome (MAS) (5 of 7 subjects treated) and therefore dose reduction (to dose level 1, $3x10^5$ CAR cells/kg) took place with a subsequent reduced incidence of HLH/MAS from 71% to 44% of subects. Forty percent of subjects that developed CRS also developed HLH/MAS clinical findings, 2 weeks from T cell infusion on average with preceding

resolution or near resolution of CRS. In 5 subjects HLH/MAS resolved without intervention. Fourteen subjects received anakinra and/or corticosteroids to treat the CD22 CAR T cell induced HLH/MAS. All subjects had resolution of HLH/MAS without an apparent impact on T cell expansion or disease response[52].

3.7.2 Neurotoxicity

A distinct syndrome of neurotoxicity can occur post infusion of CAR T cells. This syndrome consists predominantly of encephalopathy, tremor, aphasia, hallucinations, and seizures and is now termed Immune effector Cell Associated Neurotoxicity Syndrome (ICANS).[80] Nine of 43 subjects on the Phase 1 portion of PLAT-02 exhibited severe neurotoxicity, defined as any Grade 3/4 neurotoxicity, excluding headache, or $\geq$ Grade 2 seizure. Early intervention for CRS with immunomodulatory agents on the Phase 1 portion of the PLAT-02 study did not seem to impact the rates and severity of neurotoxicity: neurotoxicity was seen in 48% versus 50% of the two cohorts with similar rates of severe neurotoxicity, 22% versus 25%[81].

Similar studies of CD19 CAR T cells also report on neurotoxicity with no determination of the optimal treatment. Several adults participating in clinical trials with CAR T cells have died from neurotoxicity. The Juno JCAR15 trial, also using CD19 CAR T cells, reported 5 patient deaths due to cerebral edema following receipt of the T cells [unpublished data]. Additionally, death due to cerebral edema has been reported rarely on other CD19 CAR T cells trials. The NIH/NCI CD22 CAR T cell trial reported among the first 16 patients treated and described, 2 developed visual hallucinations, one with mild unresponsiveness, one with mild disorientation and two with mild-moderate pain. All returned to baseline 4 weeks following infusion.[51] With the incorporation of the T cell selection in the manufacturing process, a third of subjects experienced a neurologic abnormality, grade 1 or 2. However, 1 subject did develop an intracranial hemorrhage at dose level 1 ($3x10^5$ CAR cells/kg), felt to be related to the T cell therapy and infection. Neurotoxicity events were limited per report or resolved by 4 weeks post infusion[52].

3.7.3 Thrombosis and Bleeding

An emerging toxicity that is being seen with CAR T cell therapy for B cell malignancies is bleeding and thrombotic events. The exact incidence is yet to be determined but is less frequent that CRS and ICANS. Bleeding is associated with consumptive coagulopathy as well as with lower pretreatment platelet count. Subjects with grade 3 or greater ICANS have also been associated with increased risk of bleeding and thrombosis[82]. In a separate single institution study of subjects with lymphoma, there was an association between severe CRS as well as severe ICANS for risk of venous thromboembolism[83].

3.7.4 Alloreactive T cell activation

The use of expanded T cells of donor origin carries the potential risk that a portion of the cell product will consist of T cells that have an endogenous TcR that is alloreactive and capable of mediating a graft versus host response. In this study, for the post allo-HCT cohorts, the donor derived T cells are being obtained from the peripheral blood of the subject following a prior allo-HCT at a time when GVHD is quiescent, off all immunosuppression. Evidence to date suggests that GVHD recrudescence is an uncommon consequence of CAR T cell infusions when the product is derived from post-transplant patient's PBMC. It is likely that the repertoire of donor T cells engrafted in patients who fail to flair with GVHD following immune suppression withdrawal are not reactivated by their inclusion in CAR T cell adoptive therapy products. There was one case of skin GVHD noted on PLAT-02. This subject was 2.3 years from prior transplant and had tapered off GVHD medications more than a year before CAR T cell treatment. Although the infused CAR T cells cannot be formally ruled out as direct mediators of the skin GVHD, a biopsy of involved skin revealed that 9% of CD3+ T cells infiltrating the dermis were CAR-positive compared with 78% CAR-positive T cells in peripheral blood. The subject was treated with prednisone 2 mg/kg/day with resolution of GVHD and without untoward effect on the persistence of CAR T cells or BCA.

3.7.5 Potential long-term toxicity

B cell Aplasia: A potential long-term toxicity of CD22 directed CAR therapy is prolonged B cell aplasia. Since non-malignant CD22+ B cells will be subject to recognition by re-directed T cells, long-term persistence of the adoptively transferred CD22-specific cytotoxic T lymphocytes (CTLs) has the potential to cause B cell immunodeficiency. In subjects who have no curative options and who are predicted to succumb to recurrent/progressive disease, the clinical sequelae of B cell lymphopenia that can be ameliorated by subcutaneous or intravenous immunoglobulin (IVIG) therapy is an acceptable side effect of CD22 -directed immunotherapy. Prolonged ablation of normal CD20+ B cells in patients receiving rituximab therapy does not appear to result in clinically significant complications attributable to depleted numbers of normal B cells. In fact, this side effect has been reported in the literature in adult and pediatric subjects who have received CD19 CAR T cell therapy with persistence of the transferred T cells and has not been thought to be clinically relevant[84-87]. Pediatric ALL and NHL patients undergoing chemotherapy are already known to be profoundly B cell depleted, so it does not have a large effect on an already almost absent cell population[88]. If the hypogammaglobulinemia becomes clinically significant, the subject may be given IVIG as replacement therapy until B cell function returns. We have not observed significant infections following CD19 CAR therapy at our institution. Others have recently reported that there may be an advantage to maintaining higher IgG levels post B cell aplasia.[89] This trial allows intervention with cetuximab infusions to potentially ablate the infused CAR T cells that co-express EGFRt, and this is an exploratory objective of this protocol for subjects that have prolonged B cell aplasia and in whom their remission has been greater than 3 years from the time of the CAR T cell infusion.

Secondary Malignancy/Insertional Mutagenesis: Data regarding the risks of gammaretroviral vectors for T cell modification, rather than stem cell modification have been published[90]. The University of Pennsylvania analyzed 221 subject samples obtained over a decade from 43 subjects who had been enrolled in T cell trials in which CD4ζ CARs were expressed on autologous T cells (CD4 and CD8) through genetic modification with gene integration directed by gammaretroviral vectors. There was durable engraftment of the modified T cells in 212 of the samples. Through whole genome analysis, a thorough analysis of the integration sites was evaluated in 11 individuals with high-level marking. A total of 7222 unique integration sites were detected and were enriched for sites near the 5' end of a gene. There did not appear to be any clonality in the samples, and integration sites over time in the same subject varied. Additionally, there did not appear to be enrichment of integration sites near genes involved in clonal expansion or persistence, nor was there enrichment of integration sites near the 5' ends of cancer-related genes. Overall, this report had 540 subject-years without integration-mediated toxicity, placing the true adverse event rate at less than 0.0068 per person-year. These data suggest that the use of gammaretroviruses for gene-integration in T cells carries a much safer toxicity profile than when used in hematopoietic stem cells, and that T cells appear to have an inherent protection to insertional genotoxicity.

In addition to transducing T cells rather than hematopoietic stem cells, we are using a third generation SIN lentiviral vector rather than a gammaretroviral vector. Additional safety data have been published regarding the use of lentiviral vectors in clinical trials. One report detailed 65 subjects who received transduced CD4+ cells. The mean copy number was 2.3 with a range of 0.2-5.4. Additionally, all tests for replication-competent lentivirus (RCL) were negative. Previously some of these subjects had integration site analysis performed, which showed that there were >7000 unique insertion sites without evidence of enrichment near proto-oncogene 5' ends or within tumor suppressor genes[91,92]. Experience from the National Gene Vector Biorepository in testing for RCL from a variety of clinical trials was recently published, and evaluated 460 lentiviral transduced cell products from 375 subjects, all of which were negative for RCL[93] Two hundred and ninety six subjects also underwent testing at least one month after receiving a cellular product, and all were also negative for evidence of RCL. These reports suggest that lentiviral vectors are safer than gammaretroviral vectors in regards to malignant transformation potential.

In summary, we believe that the potential toxicities associated with the use of CD22- specific CAR T cell therapy are outweighed by the need to develop novel treatment for patients with life-threatening ALL and NHL.

3.8 SCRI-CAR22v2 Dosing Rationale

The manufacturing of SCRI-CAR22v2 is based on the manufacturing strategy used for another SCRI CAR T cell therapy study, PLAT-05, which uses a CD19 and CD22 specific construct. The distinct difference is that the PLAT-07 product makes use of a CD22 CAR construct rather than a CD19 and CD22 specific construct. Of note, the CD22 CAR

construct in this trial is distinct from the CD22 construct currently under investigation on the PLAT-05 trial.

The starting dose is 2 x 10^5 CAR T cells/kg which is a log below the current infusion dose of CAR T cells on PLAT-05 of 3 x 10^6 CAR T cells/kg.

4 STUDY OBJECTIVES

4.1 Primary Objectives

1. To assess the safety and toxicity of cellular immunotherapy utilizing SCRI-CAR22v2 in children and young adults who relapse with $CD22^+$ leukemia and lymphoma.
2. To describe the full toxicity profile of SCRI-CAR22v2.
3. To assess the feasibility of manufacturing and releasing SCRI-CAR22v2 from pediatric and young adult subjects who have refractory or relapsed $CD22^+$ leukemia both before and after allo-HCT.
4. Determine the efficacy of SCRI-CAR22v2 in subjects with relapsed or refractory CD22+ leukemia

4.2 Secondary Objectives

1. To determine the duration and magnitude of in vivo persistence of SCRI-CAR22v2 in the peripheral blood.
2. To assess the accumulation of SCRI-CAR22v2 in the bone marrow and cerebrospinal fluid (CSF).
3. To quantitate anti-leukemic responses by measuring changes in leukemia burden using multiparameter flow cytometry (MPF)/PCR and/or induction of CD22+ B-cell aplasia.
4. To describe the incidence of recurrence of leukemia as well as to describe recurrences as CD19+CD22+, CD19-CD22+, CD19+CD22-, and CD19-CD22-.
5. To determine the incidence of recrudescence or development of acute graft-versus-host-disease (GVHD) in treated subjects and its association with the engraftment of transferred T cells for the post-allogenic HCT cohort.
6. To assess the efficacy of infusional cetuximab in ablating SCRI-CAR22v2 to facilitate B cell recovery in treated subjects in remission with adverse events related to prolonged B cell aplasia.
7. To separately determine response rates and toxicity rates in the CR, MRD+ group and the refractory group.

4.3 Exploratory Objectives

1. To evaluate the association between host/cancer-intrinsic factors and toxicity following SCRI-CAR22v2.
2. To evaluate the association between host/cancer-intrinsic factors and response to SCRI-CAR22v2.
3. Determine the rates of infectious complications in subjects who have received SCRI-CAR22v2.

5 ENROLLMENT AND ELIGIBILITY

5.1 Enrollment

Upon consent for participation in an SCRI immunotherapy clinical trial, subjects will be entered into the Immunotherapy Registration Portal. A unique Registration ID will be assigned to each potential study subject, and demographic and general eligibility information will be collected.

All subjects who are consented will be entered into a study-specific database following review of eligibility documentation.

5.2 Eligibility

5.2.1 Inclusion criteria

1. Subjects age ≤ 30 years. The first two enrolled subjects must be ≥ 18 years of age.
2. Evidence of refractory or recurrent CD22+ leukemia or lymphoma as indicated by:

   a. Leukemia (must meet at least one of the below criteria):
   - If post-allogeneic hematopoietic stem cell transplant (HCT):
     - Recurrence defined as ≥ 0.01% disease in the marrow, OR
     - Recurrent isolated extramedullary disease
   - If no history of allogeneic HCT, one of the following:
     - Second or greater relapse, with or without extramedullary disease (subjects with isolated extramedullary disease are eligible),
     - First marrow relapse at end of 1st month of re-induction with marrow having ≥0.01% blast by morphology and/or MPF, with or without extramedullary disease,
     - Primary Refractory as defined as having >5% disease in the marrow by MPF after 2 or more separate induction regimens, OR
     - Subject has indication for allogeneic HCT but has been deemed ineligible, including subjects who have persistent MRD prior to HCT.
   - If previously treated with B cell antigen targeting CAR T cell immunotherapy, subject meets one of the following:
     - evidence of persistent or recurrent CD22+ leukemia at any point after infusion of prior CAR T cell product.

   b. Lymphoma (must meet at least one of the below criteria)
   - Relapsed and/or refractory with no known curative therapy available, defined as one of the following:
     - Relapsed or refractory disease after ≥ 2 treatment regimens including, at a minimum:

- anti-CD20 monoclonal antibody (unless tumor is determined to be CD20 negative or the subject has a diagnosis of lymphoblastic lymphoma)
- anthracycline-containing regimen

- Not eligible to proceed with an autologous transplant secondary to disease status or other medical reason
- Relapsed or refractory disease post-autologous or allogenic transplant

- If previously treated with B cell antigen targeting CAR T cell immunotherapy, subject meets one of the following:
  - Evidence of persistent or recurrent CD22+ lymphoma at any point after infusion of prior CAR T cell product.

3. Able to tolerate apheresis, or subject with sufficient existing apheresis product or T cells for manufacturing investigational product.
4. Life expectancy ≥ 8 weeks
5. Lansky performance status score of ≥ 50 for subjects <16 years of age or Karnofsky score ≥ 50 for subjects ≥ 16 years. Subjects who are unable to walk because of paralysis, but who are up in a wheelchair, will be considered ambulatory for purposes of assessing performance status
6. If a subject does not have a previously obtained apheresis product that is acceptable and available for manufacturing of CAR T cells, the subject must discontinue all anti-cancer agents and radiotherapy and, in the opinion of the investigator, have fully recovered from significant acute toxic effects of all prior chemotherapy, immunotherapy, and radiotherapy:
   a. *Chemotherapy and biologic agents:* All chemotherapy and biologic therapy not specifically mentioned below must be discontinued ≥ 7 days prior to enrollment, with the exception of intrathecal chemotherapy and maintenance chemotherapy (for the subset of subjects who relapse during maintenance), both of which may be administered at any point pre-enrollment.
   b. *Steroid use:* All systemically administered (i.e. PO or IV) corticosteroid therapy (unless physiologic replacement dosing) must be discontinued ≥ 7 days prior to enrollment
   c. *Tyrosine Kinase Inhibitor (TKI) use:* All TKIs must be discontinued ≥ 3 days prior to enrollment
   d. *Hydroxyurea:* must be discontinued ≥ 1 day prior to enrollment.
   e. *Prior CAR T cell therapy:* must be at least 30 days from most recent CAR T cell infusion
7. Adequate organ function as indicated by:
   a. Renal: Serum creatinine ≤ 1.5 X the upper limit of normal (ULN) based on the following:

Table 5-1 Serum Creatinine Values

Maximum Serum Creatinine (mg/dL),		
Age	Male	Female
1 to < 2 yrs	0.6	0.6
2 to < 6 yrs	0.8	0.8
6 to <10 yrs	1	1
10 to < 13 yrs	1.2	1.2
13 to < 16 yrs	1.5	1.4
≥ 16 yrs	1.7	1.4

   b. Hepatic: Total bilirubin ≤ 3 times ULN for age OR conjugated bilirubin ≤ 2 mg/dL AND ALT (SGPT) ≤ 5 times ULN
   c. Cardiac: Shortening fraction ≥ 28% OR ejection fraction ≥ 50% as measured by echocardiogram
   d. Respiratory: Oxygen saturation ≥ 90% on room air without supplemental oxygen or mechanical ventilation
8. Laboratory values meet the following criteria:
   a. Subjects requiring apheresis: Absolute Lymphocyte Count (ALC) ≥ 100 cells/uL
   b. Virology Testing negative within 3 months prior to enrollment, to include:
      i. HIV antigen & antibody
      ii. Hepatitis B surface antigen
      iii. Hepatitis C antibody OR if positive, Hepatitis C PCR is negative
9. If subject is of child-bearing or child-fathering potential, must agree to use highly effective contraception (Appendix 9: Highly Effective Contraception) from the time of initial consent through 12 months following the infusion of investigational product on this trial.
10. Subject and/or legally authorized representative has signed the Informed Consent Form for this study

5.2.2 Exclusion criteria

1. Active malignancy other than disease under study
2. History of symptomatic CNS pathology or ongoing symptomatic CNS pathology requiring medical intervention, including paresis, aphasia, cerebrovascular ischemia/hemorrhage, severe brain injury, dementia, cerebellar disease, organic brain syndrome, psychosis, coordination or movement disorder (subjects with non-febrile seizure disorder controlled on anti-epileptic medication and without seizure activity within 3 months are eligible)
3. CNS involvement of leukemia or lymphoma that is symptomatic and in the opinion of the investigator, cannot be controlled during the interval between enrollment and CAR T cell infusion

4. Subjects with uniform expression of CD19 on their malignant cells who are eligible but have not attempted CD19 directed CAR T cell therapy
5. If history of allogeneic stem cell transplant: active GVHD, or receiving immunosuppressive therapy for treatment or prevention of GVHD within 4 weeks prior to enrollment
6. Presence of active severe infection, defined as:
    a. positive blood culture within 48 hours of enrollment, OR
    b. fever above 38.2° C, AND clinical signs of infection within 48 hours of enrollment
7. Primary immunodeficiency syndrome
8. Subject has received prior virotherapy
9. Pregnant or breastfeeding
10. Subject and/or legally authorized representative unwilling to provide consent/assent for participation in the 15-year follow-up period, required if CAR T cell therapy is administered
11. Presence of any condition that, in the opinion of the investigator, would prohibit the subject from undergoing treatment under this protocol

6 DRUG INFORMATION

6.1 Manufacturing of SCRI-CAR22v2

Manufacturing of SCRI-CAR22v2 will be conducted in the SCRI Therapeutic Cell Production Core (TCPC). At the end of the culture, cells will be harvested, washed and formulated in cryopreservation media, and transferred to cryopreservation storage. Cryopreserved cells will be stored in vapor phase in a controlled access LN_2 freezer maintained in the TCPC facility until released for clinical use. On the day of T cell product infusion cryopreserved unit(s) will be thawed at the bedside and will be immediately available for infusion.

6.2 SCRI-CAR22v2 cell product infusion

Subject may undergo CAR T cell infusion in the outpatient or inpatient setting. When clinically prudent, subjects may be admitted to the hospital following the CAR T cell infusion for observation and monitoring if they exhibit minor symptoms which, if to worsen, could place the subject at risk of an adverse medical outcome.

In addition to institutional guidelines for infusion of cellular products, subjects are to receive the CAR T cell product according to the following guidelines:

- Prior to CAR T cell product administration (in instances of documented allergy or sensitivity to any of the below pre-medications clinical discretion may be used for appropriate substitution):
    - Required: acetaminophen
        - Recommended dosing: 12.5 mg/kg (maximum dose 650 mg), PO
    - Required: diphenhydramine
        - Recommended dosing: 1 mg/kg (maximum dose 50 mg), IV or PO
    - Optional: ondansetron
        - Recommended dosing: 0.15 mg/kg (maximum dose 8 mg), IV or PO
- Thawed, formulated CAR T cells will be infused as rapidly as tolerated through a central venous catheter and should be infused by gravity or syringe push.
- Microaggregate filters and leukodepletion filters must not be used to infuse CAR T cell product

6.3 Definition of Dose Limiting Toxicity

Disease progression, and toxicities of any grade normally expected with apheresis or lymphodepletion will not be considered a DLT with respect to protocol continuation, or to the MTD determination of T cell dose.

The following are considered DLT's:

- Any Grade 3 or higher toxicity; and designated as definitely, probably or possibly related to the infusion of the T cells; and occurring within 28 days of T cell infusion, except for the following:

  Non-DLT toxicities (usually occurring up to 3 weeks after completion of the T cell infusion):

  - Grade 3 chills lasting up to 5 days
  - Grade 3 Cytokine Release Syndrome lasting up to 72 hours
  - Grade 3 or 4 lymphopenia
  - Grade 3 or 4 leukopenia
  - Grade 3 or 4 anemia
  - Grade 3 or 4 thrombocytopenia
  - Grade 3 pain (including headache) lasting up to 2 weeks
  - Grade 3 or 4 Tumor Lysis Syndrome lasting up to 2 weeks
  - Grade 3 liver or kidney dysfunction lasting up to 1 week

- Any toxicity requiring the use of cetuximab (or other immunosuppressive agents other than corticosteroids, for example, but not limited to anti-thymoglobulin, calcineurin inhibitor or chemotherapy) to ameliorate side effects attributable to the infusion of T cells, and occurring within 28 days of T cell infusion.

7 TREATMENT PROGRAM

7.1 Apheresis for T cell isolation

In subjects who do not already have an apheresis product available for use in manufacturing, they will undergo apheresis to obtain T cells from which individualized CAR T cell therapy will be manufactured. Apheresis may take place in either an outpatient or inpatient setting and will be performed per institutional standard operating procedure. After undergoing medical clearance, subjects will undergo apheresis with a target collection of 1 x 10^9 total nucleated cells. Subjects may undergo a repeat apheresis procedure if necessary due to a manufacturing failure if it is felt to be likely by the Principal Investigator to yield a successful product.

7.1.1 Requirements for apheresis

Subjects with active, severe, infection may not undergo apheresis. For the purpose of this trial, active, severe infection is defined as:

- Positive blood culture within 48 hours of apheresis, OR
- Fever > 38.2 °C AND clinical signs of infection within 48 hours of apheresis

7.2 Bridging Therapy

Between the time of apheresis and CAR T cell product infusion, subjects may return to the care of their treating physician. Additional therapy aimed at controlling disease burden to allow the subject to meet criteria for CAR T cell infusion may be given. Investigational agents and CD22-directed agents are not allowed during this time. Refer to Table 7-1 for Bridging Therapy wash-out requirements prior to CAR T cell infusion. Information regarding Bridging Therapy will be recorded in the CRFs.

7.3 Recommendations for lymphodepletion regimens

Lymphodepletion is required in all subjects, unless they have a medical contraindication to receiving it. For subjects with a contraindication to lymphodepletion, they must have an ALC of < 500 cell/µl. When administered, lymphodepletion chemotherapy must be completed at least 48 hours prior to infusion of CAR T cells. The following are general guidelines for lymphodepleting regimens that may be employed immediately prior to CAR T cell therapy.

The preferred regimen is the following combination of fludarabine and cyclophosphamide (flu/cy):

- Fludarabine 30 mg/m^2 IV once daily x 4 doses (Days 1-4); and
- Cyclophosphamide 500mg/m^2 IV once daily x 2 doses (Days 3-4)

Subjects may receive a different lymphodepleting regimen if it is felt to be in the best interest of the subject. Recommendations are provided below. Lymphodepleting regimens not included here may also be used after consulting with the study team.

- Fludarabine
- Fludarabine/Cytarabine
- Cyclophosphamide/Etoposide
- Single Agent Cyclophosphamide:
  - High Dose Cyclophosphamide (2-4g/m^2) with MESNA

7.4 SCRI-CAR22v2 Dosing Regimen

The primary goal of the Phase 1 portion of this study is to evaluate the feasibility and safety of a single infusion of SCRI-CAR22v2. The cohort dose levels are as follows:

- Dose Level 1: Target dose 2 x 10^5 # of CAR $^+$ T cells/kg (range > 1x10^5 to 2x10^5) up to a maximum of 25 x 10^6 # CAR T cells

- Dose Level 2: Target Dose 5x10^5 # of CAR$^+$ T cells/kg (range >3 x10^5 to 5x10^5) up to a maximum of 50 x 10^6 CAR T cells

- Dose Level 3: Target Dose 1x10^6 # of CAR$^+$ T cells/kg (range >7.5 x10^5 to 1x10^6) up to a maximum of 100 x 10^6 CAR T cells

CAR T cell product dose is calculated based on weight obtained at time of pre-lymphodepletion procedures. For subjects who do not receive lymphodepletion, the dose of investigation product administered will be based on weight obtained within 2 weeks prior to the scheduled infusion (see Appendix 2:)

Dosing assignment will occur after enrollment and prior to CAR T cell infusion. Dosing will initiate at Dose Level 1. There will be a minimum of 28 calendar days between each subject infusion for the first 2 subjects at each dose level, followed by a minimum of 14 days before the 3rd subject at a dose level. A 3+3 statistical design will then be employed to ultimately determine the MTD and recommended phase 2 dose (RP2D). Detailed rules for dose escalation/de-escalation and termination of dose-finding are given in Section 10.2.1.2

7.4.1 Requirements for SCRI-CAR22v2 infusion

Within 2 days prior to receiving the initial CAR T cell infusion, the subject will be evaluated to confirm the following criteria are met. Documented verification that the subject is eligible to proceed per below listed criteria is required.

- Subject is ≥ 7 days from receiving supra-physiologic dosing of systemic corticosteroids. Glucocorticosteroid physiologic replacement therapy for management of adrenal insufficiency is allowed.

- If lymphodepleting chemotherapy was not administered, ALC is <500 cells/µl
- If administered, lymphodepletion chemotherapy was completed at least 48 hours prior to the infusion of CAR T cells
- Subject has adequate organ function as indicated by:

Renal: Serum creatinine ≤ 1.5X ULN (see section 5.2.1, Table 5-1 Serum Creatinine Values)

  - Hepatic:
    - Total bilirubin ≤ 3 times ULN for age OR conjugated bilirubin ≤ 2 mg/dL, AND
    - ALT (SGPT) ≤ 5 times ULN.
  - Adequate respiratory function defined as not requiring supplemental oxygen or mechanical ventilation, oxygen saturation 90% or higher on room air.
  - Cardiac: If a subject received anthracycline chemotherapy after enrollment or had an ECHO performed after enrollment demonstrating EF of <50% or SF<28%; they must demonstrate adequate cardiac function, defined as shortening fraction ≥28% or an ejection fraction ≥50% by echocardiogram, within 14 days prior to lymphodepletion.
- No evidence of active severe infection, defined as:
  - positive blood culture within 48 hours of enrollment, OR
  - fever above 38.2° C, AND clinical signs of infection within 48 hours of enrollment.
- No evidence of clinically significant encephalopathy/new focal neurologic deficits
- If subject has a history of an allogeneic HCT, no evidence of active GVHD
- The following treatments must be discontinued for the specified duration (wash-out period) prior to infusion of the CAR T cell product, and subject must have recovered from acute therapy-associated toxicities.

Table 7-1 Treatment wash out requirements

Treatment	Wash-out Period (prior to CAR T cell product infusion)
Cranial radiation therapy (inclusive of TBI)	≥ 6 weeks
Cytotoxic chemotherapy (if not receiving lymphodepleting chemotherapy)	≥ 2 days
Tyrosine Kinase Inhibitor	≥ 7 days

7.5 Follow-up

Subjects will be followed for up to 15 years after CAR T cell infusion.

7.5.1 Active Follow-up

After CAR T cell infusion, subjects will be closely monitored per protocol through Day 28.

7.5.2 Long-Term Follow-up

Subjects who receive CAR T cells will be followed for up to 15 years from the time of the most recent CAR T cell product infusion, to capture delayed AEs related to the use of lentivirally transduced T cells as required by the FDA. Additional information including disease evaluation and requirements for immunoglobulin replacement will also be captured if relevant. In the subset of subjects with ongoing B cell aplasia, infectious complications will also be collected. Follow-up information may be provided by the subject's primary care physician.

Subjects who subsequently enroll on a separate lentiviral gene cell therapy trial will undergo FDA-mandated delayed adverse event monitoring and long-term follow-up testing in association with the separate gene cell therapy trial, however will be followed for survival on PLAT-07.

8 SUPPORTIVE CARE AND MANAGEMENT OF TOXICITIES AND COMPLICATIONS

8.1 Concomitant medication/supportive care

8.1.1 Anti-epileptic drugs

If a subject shows evidence of CRS requiring tocilizumab or dexamethasone/prednisone, or has any signs of mild neurotoxicity and is not already receiving ant-epileptic drugs (AED), an AED should be started and continued until 21 days following the CAR T cell infusion. The recommended first line AED is levetiracetam (Keppra).

8.1.2 Blood product support

All blood products will be transfused per institutional standards.

It is recommended that platelet transfusions be given to maintain a platelet count ≥ 10,000 mm^3 prior to initial CAR T cell infusion. Platelet transfusions should be given to maintain a platelet count of ≥ 50,000 mm^3 during periods of Grade 2-4 CRS.

Packed red blood cells should be given to maintain a hematocrit of ≥ 25% during periods of Grade 2 – 4 CRS, unless clinically the subject has a higher established transfusion threshold. Cryoprecipitate should be given to maintain fibrinogen > 150 mg/dL.

8.1.3 Antimicrobial prophylaxis or therapy

If lymphodepletion therapy is given, pneumocystis jiroveci pneumonia (PJP) prophylaxis should be given per institution standard. It may be prudent to avoid sulfamethoxazole/ trimethoprim due to count suppression and preference may be given to pentamidine. The management of infections in these immuno-compromised subjects will follow institutional standards but may be individualized as clinically indicated. Institutional standards for infectious diseases will guide addition of antimicrobial agents in cases of persistent or recurrent fever.

Additionally, if the CAR T cell product has a positive culture which is discovered after being infused into the subject, blood cultures will be drawn and appropriate antimicrobial coverage will be initiated. If the subject's blood cultures remain negative for 5 days and the subject remains clinically well, antimicrobials may be discontinued.

8.1.4 Replacement of immunoglobulin

Subcutaneous or intravenous immunoglobulin (SCIG or IVIG) should be administered when quantitative gamma immunoglobulins (IgGs) are below 400 mg/dL, or according to institutional standards.

8.1.5 Prohibited medications

Subjects are prohibited from receiving investigational agents other than the agent under study in this protocol from enrollment through Day 28 following CAR T cell infusion.

Between enrollment and apheresis, subjects are prohibited from receiving disease directed therapy including corticosteroids, except when administered as physiologic replacement dosing.

Following apheresis and prior to the receipt of CAR T cell therapy, subject may receive disease directed therapy as bridging therapy, however they may not receive any CD22 targeting therapy during this time. Please refer to Section 7.2 Bridging Therapy for washout requirements of medications prior to CAR T cell therapy.

The following agents are not allowed once CAR T cell therapy commences through 28 days following the last CAR T cell infusion, unless the subject has discontinued protocol therapy for toxicity or tumor progression and requires such therapy for clinical care:

- Anti-tumor directed chemotherapy
- Systemic immunosuppresive agents except for those listed below:
  - physiologic doses of systemic corticosteroids;
  - systemic immunosuppressive agents as outlined in Section 8, Management of Toxicities and Complications
- Immunotherapy (other than the protocol-specified CAR T cell infusions)
- Other investigational agents, unless used to treat or prevent symptoms related to CAR T cell infusion(s) administered on this protocol

8.2 Symptoms Associated with Apheresis

Side effects that may occur during cell collection include nausea, vomiting, fainting or dizziness, seizures, skin rash, hives, flushing (redness and warmness of the skin, usually the face), blood loss, and infection. Tingling of the lips, muscle cramping, and, very rarely, changes in heart rhythm, may occur. These symptoms may be prevented or made milder by giving calcium supplements, either by mouth or IV during the apheresis procedure. Very rarely (< 1 in 1,000 procedures) clotting may occur in the apheresis machine or in the subject and is potentially life-threatening. To reduce the risk of clotting, acid-citrate-dextrose (ACD) and heparin may be given during the apheresis procedure. ACD may increase the risk of bleeding and may cause temporary tingling of the lips and limbs, muscle cramping, seizures, or changes in heart rhythm. Heparin may also increase the risk of bleeding. Transfusions of both RBC and platelets may be required surrounding the procedure.

8.3 Symptoms Associated with CAR T Cell Infusion

Mild, transient symptoms have been observed with CAR T cell therapy including fevers, chills, rigors, headache, and, rarely, nausea, vomiting, hypotension, and pulmonary toxicity. The management of these symptoms is outlined below.

- *Fever, chills and temperature elevations >38.2 ° C* may be managed with additional acetaminophen as clinically indicated. Additional methods such as cooling blankets may be employed for fevers resistant to these measures. All subjects who develop fever and/or chills should have a blood culture drawn and be admitted for IV antibiotics and supportive care.
- *Headache* may be managed with acetaminophen. If unresponsive to acetaminophen, manage with good clinical judgment.
- *Nausea and vomiting* may be treated with ondansetron IV or PO, as well as additional standard anti-emetic treatment per subject/provider preference.
- *Hypoxemia* may be managed by standard clinical practice
- *Hypotension:*
    - Transient hypotension may initially be managed by intravenous fluid administration; however, subjects with persistent hypotension may require transfer to the intensive care unit (ICU) for definitive medical treatment.
    - If significant hypotension occurs during the CAR T cell infusion, the infusion should be immediately suspended. Significant hypotension is defined as symptomatic and/or systolic blood pressure < 80 mm/hg for age > 12 years, < 70 mm/hg for age < 12 years, or a 15% drop from baseline, whichever value is lower.
    - Treatment for significant hypotension will follow institution standard practice.

If the CAR T cell infusion is stopped before completion and the symptoms causing cessation return to baseline within 30 minutes, the CAR T cell infusion may be restarted; all product must be infused prior to the expiration time/date listed on the syringe label.

If the CAR T cell infusion is terminated due to acute toxicity occurring during the infusion, the residual CAR T cell product should be returned to the TCPC for analysis. Investigation of possible causes of observed symptoms should proceed and, if necessary, additional medical treatment should be instituted.

8.4 Symptoms Attributable to Expansion of the CAR T Cells

8.4.1 Management of cytokine release syndrome and neurotoxicity

All subjects for whom there is concern for CRS or neurotoxicity will be admitted to the hospital for observation. In subjects who develop CRS during *in vivo* expansion of CAR T cells, additional clinical laboratory testing will be requested (see Section 9.2.5 CRS labs). If a subject is suspected of having CRS, additional samples may be sent for clinical cytokine

analysis per treating physician discretion. Subjects may receive cytokine-directed therapy for symptom control including, but not limited to, tocilizumab. The use of steroids may be given to prevent a more serious toxicity. Table 8-1 provides guidelines for CRS management.

All subjects admitted with either CRS or neurotoxicity will undergo daily neurologic examinations. For subjects who develop mild neurologic manifestations (ICANS Grade 1), symptomatic care and levetiracetam are recommended. Discussion with the Principal Investigator or designee is recommended. For subjects with worsening neurologic changes, the addition of corticosteroids should be considered (ICANS Grade 3), with initial dosing recommendations of dexamethasone 5-10mg IV q 6-12 hours until resolution of symptoms. For progressive/severe toxicity (ICANS Grade 4), high dose methylprednisolone is recommended (20 mg/kg, up to max dose of 1g) with continuation daily until resolution of symptoms. Tocilizumab (8-12 mg/kg IV) or other cytokine-directed therapies may be used based on clinical judgment but is not recommended if CRS is not concurrently present. Cerebrospinal fluid (CSF) assessments and CNS imaging (MRI preferred) should be considered when clinically available and if obtained, results will be collected.

Table 8-1 Recommended symptom management for CRS

Symptom Related to CRS	Suggested Intervention
Fever	Acetaminophen (12.5 mg/kg) PO/IV up to every 4 hrs
Persistent fever ≥ 39° C for 6 hrs that is unresponsive to acetaminophen	Tocilizumab (8-12 mg/kg) IV
Persistent fevers ≥ 39° C after tocilizumab	Dexamethasone 5-10 mg IV/PO up to every 6-12 hrs with continued fevers
Recurrence of symptoms 48 hrs after initial dose of tocilizumab	Tocilizumab (8-12 mg/kg) IV
Hypotension	Fluid bolus, target hematocrit > 24%
Persistent/recurrent hypotension after initial fluid bolus (within 6 hrs)	Tocilizumab (8-12 mg/kg) IV
Use of low dose vasopressors for hypotension for longer than 12 hrs	Dexamethasone 5-10 mg IV/PO up to every 6 hrs with continued use of vasopressors
Initiation of higher dose vasopressors or addition of a second pressor for hypotension	Dexamethasone 5-10 mg IV/PO up to every 6 hrs with continued use of vasopressors
Initiation of oxygen supplementation	Tocilizumab (8-12 mg/kg) IV
Increasing respiratory support with concern for impending intubation	Dexamethasone 5-10 mg IV/PO up to every 6-12 hrs
Recurrence/Persistence of symptoms for which tocilizumab was given ≥ 48 hrs after initial dose was administered	Tocilizumab (8-12 mg/kg) IV

8.4.2 Management of non-CRS/non-neurologic acute toxicity associated with expansion of infused CAR T cells

Subjects who develop medically significant toxicity attributable to the infused CAR T cell product will be hospitalized for observation and treatment. Subjects who develop a new toxicity ≥ Grade 3 which is probably or definitely attributable to the CAR T cell infusion, and, in the opinion of the Principal Investigator or designee puts the subject at significant risk of an untoward outcome if measures are not taken to ameliorate the toxicity, should be given corticosteroids.

- Recommended steroid dose schedule: Methylprednisolone dose of 20 mg/kg (max dose of 1g) given up to once every 24 hours should be considered in subjects with severe toxicity. Alternatively, dexamethasone may be given in place of prednisone. All subjects will be hospitalized for at least the first 72 hours after receiving corticosteroids.

- If the toxicity requiring treatment is concerning for macrophage activation syndrome, anakinra should also be employed in conjunction with methylprednisolone. Starting doses of anakinra should be 2mg/kg every 6-12 hours for severe MAS.

8.4.3 Ablation of T cells

Cetuximab therapy may be initiated for subjects experiencing a new systemic toxicity, which is probably or definitely attributed to the infused CAR T cell product, which is:

- ≥ Grade 3 toxicity lasting greater than 48 hours, and is not controlled by medical intervention (including steroids or cytokine-directed therapy), AND in the opinion of the PI or designee cannot be controlled putting the subject at significant risk of an untoward outcome if measures are not taken to ameliorate the toxicity, OR
- Any duration or grade of toxicity which, in the opinion of the PI or designee, cannot be controlled and puts the subject at significant risk of an untoward outcome if measures are not taken to ameliorate the toxicity, OR
- Subjects whose molecular studies indicate a lymphoproliferative disorder is arising from the CAR T cells, OR
- Subjects with prolonged B cell aplasia due to persistence of CAR T cells who require chronic immunoglobulin replacement in the setting of a durable complete disease remission of >3 years

The Study Chair or designee must be consulted prior to administering cetuximab. Cetuximab is to be administered according to the current package insert. Dosing recommendations are as follows:

- Subjects Age ≥ 18 years based FDA approved dosing: loading dose of 400 mg/m^2 IV, followed by 250 mg/m^2 IV weekly for a total of 4 doses.
- Subjects Age <18 years based on phase I data in children: [94] dose of 250 mg/m^2 IV administered over 1 hour weekly for a total of 4 doses.

Pretreatment with IV diphenhydramine is recommended 30-60 minutes before each dose of cetuximab.

For all subjects receiving cetuximab, CAR T cell persistence should be determined prior to each cetuximab dose. Subjects should have up to 15 mL of blood drawn for correlative studies samples pre-ablation and 1, 3, 7, 10, 14, and 28 days after ablation. Time points are based off of the first dose, and are not repeated with each dose. Up to a total of 4 weekly doses may be given. Any further cetxuximab therapy, if deemed necessary by the Study Chair or designee, will be administered only after consultation with the FDA.

All Correlative Studies samples drawn in response to cetuximab administration have a ± 3 day window, however a distinct sample must be drawn for each time point required by the protocol; samples may not be shared across time points: for instance, 1 sample drawn on Day

5 following cetuximab dosing could not be used for both Day 3 and Day 7 despite being within the draw window.

Additional measures may also be taken to resolve the toxicity should the protocol-specified cetuximab treatment plan fail to abate the side effects associated with the CAR T cell infusion such as, but not limited to, immunosuppressive medications such as ATG/Campath and calcineurin inhibitors, or chemotherapy agents with immunosuppressive properties, or other immunosuppressive agents.

Please see the SCRI-CAR22v2 Investigator's Brochure for detailed safety information.

9 STUDY PROCEDURES AND ASSESSMENTS

9.1 Clinical Assessments

Refer to the Schedule of Procedures (Appendix 2: for a summary of required study activities.

9.1.1 Informed Consent

Prior to conducting any tests or procedures performed solely for the purposes of the study, written informed consent, and assent if applicable, must be obtained from the subject or subject's legal representative.

9.1.2 Demographics

Demographic information (date of birth, gender, race, ethnicity) will be uploaded from the Immunology Registration Portal.

9.1.3 Medical History and Active Medical Conditions

Relevant medical history and active medical conditions, including history and treatment of leukemia or lymphoma, will be obtained at Screening. Active medical conditions will also be obtained at the pre-T cell infusion evaluation to establish baseline adverse events prior to infusion.

9.1.4 Performance Status

Lansky (for subjects < 16 years of age) or Karnofsky (for subjects ≥ 16 years of age) performance status will be assessed at Screening. Subjects who are unable to walk because of paralysis, but who are up in a wheelchair, will be considered ambulatory for purposes of assessing performance status. Reference Appendix 3: for performance status assessment scales.

9.1.5 Physical Examination, Vital Signs

A physical examination (PE) including weight, and vital signs (VS, including pulse, temperature, respiratory rate, and blood pressure) will be performed as noted in the Schedule of Procedures. Height will be obtained at screening.

9.1.6 Pulse Oximetry

Pulse oximetry will be performed as noted in the Schedule of Procedures.

9.1.7 Graft Versus Host Examination

A complete graft versus host review will occur at the time of regularly scheduled visits as indicated in the Schedule of Procedures and include history, physical exam and relevant lab work if clinically indicated. Refer to Appendix 4: for GVHD Grading.

9.1.8 Neurologic Examination

A complete neurological exam will be performed as indicated in the Schedule of Procedures. This exam should address cranial nerve findings and the presence or absence of

encephalopathy, confusion, dizziness, lethargy, seizures, tremors, impaired speech, impaired purposeful movement, and impaired concentration.

9.1.9 Echocardiogram

An echocardiogram (ECHO) will be performed at Screening for all subjects and prior to T cell infusion for subjects who received anthracycline-containing Bridging Therapy or for subjects who have had an ECHO post enrollment with abnormal function as indicated on the Schedule of Procedures.

9.1.10 Concomitant Medications

All concomitant medication and therapies will be documented at the time of apheresis and prior to the initial CAR T cell infusion and at the time points indicated on the Schedule of Procedures from initial CAR T cell infusion through 28 days following the infusion.

9.1.11 Adverse Events

Information regarding Grade ≥2 AEs will be captured at the time of T cell infusion evaluation through Day 28 per Section 11 Adverse Events and Serious Adverse Events. In addition, Grade 1 CRS and Grade 1 ICANS or other Grade 1 neurotoxicity are considered AEs of interest and will be captured and documented. Related AEs will continue to be followed past Day 28 until resolution if possible. This study will utilize the National Cancer Institute (NCI) Common Terminology for Adverse Events (CTCAE) for toxicity reporting and grading, except for CRS and ICANS which will be assessed using the protocol specific CRS and ICANS Grading Scale (see Section 11.3.1. Grading of Adverse Events). The study team should have access the CTCAE v5 which can be downloaded from the Cancer Therapy Evaluation Program (CTEP) website (http://ctep.cancer.gov). Refer to Section 11 for information on reporting AEs.

9.1.12 Hospitalization/ICU and ANC Recovery

The study team will record any hospitalization or admission to the ICU at any time between initiation of SCRI-CAR22v2 and Day 28 or removal from active follow-up, whichever is earlier. The relationship to treatment with SCRI-CAR22v2 will be assessed by the PI or sub-investigator for all admissions.

The date and ANC value when ANC first recovered to >500 cells/µL following SCRI-CAR22v2 infusion will be recorded.

9.2 Laboratory Studies

9.2.1 Pregnancy Test

Female subjects of childbearing potential will have urine or serum pregnancy test at screening.

Additional pregnancy tests will be performed at any visit in which pregnancy status is in question. A serum pregnancy test will be performed in the event of a positive or equivocal urine pregnancy test result.

9.2.2 Hematology

Complete blood count including hemoglobin, hematocrit, red blood cell count, white blood cell count, white blood cell differential, and platelet count will be obtained at according to the Schedule of Procedures.

9.2.3 Blood Chemistries

Serum sodium, potassium, chloride, bicarbonate, BUN, creatinine, alanine aminotransferase (ALT/SGPT), total bilirubin, conjugated bilirubin, calcium, magnesium, phosphorus, uric acid and LDH will be obtained according to the Schedule of Procedures.

9.2.4 Inflammatory Markers

Ferritin and CRP will be obtained according to the Schedule of Procedures

9.2.5 CRS labs

CRP, LDH, ferritin, D-Dimer, PT, PTT, fibrinogen, and absolute lymphocyte count will be obtained daily during periods of Grade 2 to 4 CRS; see Schedule of Procedures

9.2.6 Immunoglobulin G

Serum Immunoglobulin (IgG) will be assessed at the time points noted in the Schedule of Procedures.

9.2.7 Bone Marrow

Bone marrow aspiration with or without biopsy will be obtained for response assessment (Disease Response Criteria for Leukemia and Disease Response Criteria for Lymphoma), and will be performed according to standards of care at time points indicated in the Schedule of Procedures. Bone marrow specimens will be sent for morphologic evaluation and determination of minimal residual disease (MRD) status as detected by multi-parameter flow (MPF) or polymerase chain reaction (PCR). Cytogenetic evaluation must be done on at least one marrow specimen with the current relapse and if previously obtained, does not need to be repeated for the study.

9.2.8 Cerebrospinal Fluid (CSF)

CSF sampling by standard clinical procedure will be performed according to standards of care. CSF will be assessed for cell count, glucose, protein and cytology, except at screening, when glucose and protein are not required.

9.2.9 Virology

Human immunodeficiency virus (HIV) antigen and antibody, Hepatitis B surface antigen, and Hepatitis C antibody testing will be performed prior to enrollment. If Hepatitis C

antibody testing is positive, quantitative PCR (qPCR) will be performed. Results of virology testing obtained up to 3 months prior to enrollment will be accepted.

9.2.10 Correlative Studies

Refer to the study specific lab manual for requirements regarding all correlative studies samples. Correlative specimens will be processed for prospective testing as listed below:

- Specimens may be processed for molecular analysis of CAR T cell persistence and/or flow cytometric analysis in conjunction with T cell surface markers.
- These samples may also be used to detect the *in vitro* anti-CD22 activity of the persisting CAR T cells and for serum cytokine analysis.
- Additionally, DNA based testing may be done to detect low levels of leukemia cells.
- Non – T cell immune cells will be assessed to look for determinants of and/or contribution to toxicity and efficacy. This will be done using assays which may include RNA and DNA sequencing, phenotypic analysis with multiparameter flow cytometry and/or CyTOF and/or gene expression profiling.
- Serum may be processed for cytokine analysis and immunoglobulin specificity assessment

- *Peripheral blood*: Peripheral blood samples will be drawn at the timepoints specified in the Schedule of Procedures (Appendix 2:) and sent to CSL.
- *Bone marrow unilateral aspirate:* Bone marrow unilateral aspirate will be sent to CSL for correlative studies testing at the timepoints indicated in the Schedule of Procedures. Bone marrow samples for CSL may be requested for non-protocol mandated bone marrow assessments done for clinical indications.
- *Cerebrospinal fluid:* CSF will be sent to CSL at timepoints indicated in the Schedule of Procedures. CSF samples for CSL may be requested for non-protocol mandated lumbar punctures done for clinical indications.
- *Other:*
  - Per Symptoms Associated with CAR T Cell Infusion if a subject is suspected of having CRS, blood samples may be requested up to once per day during the time of illness in order to do cytokine and T cell analysis.
  - If peripheral blasts are present in the apheresis sample, they may be frozen for *in vitro* or *in vivo* experiments to evaluate the ability of the CAR T cells to target the subject's primary leukemic cells.
  - Any material in excess of that needed for correlative studies will be retained for potential additional analysis related to this trial.
  - If subject undergoes a tissue biopsy for clinical purposes, sample may be requested by the Sponsor to be sent to CSL for evaluation of CAR T cells, tumor cells or immune biomarkers.

9.3 Imaging Studies

Disease-specific standard of care radiographic imaging for assessment of cancer including anatomic imaging with CT and functional imaging with FDG-PET will be performed according to the Schedule of Procedures as clinically indicated for the subject's disease, and may also be obtained at additional time points as clinically indicated.

9.4 Post-Treatment Long-Term Follow-Up Testing

At the time points specified in the Schedule of Procedures (Appendix 2, Table 2 Long-Term Follow-Up, Years 1 through 5) up to 15 mL of peripheral blood will be drawn and sent to CSL and if relevant, will be tested for persistence of CAR T cells, clonality, and replication-competent lentivirus (RCL) through year 1. During years 2 through 15 samples will be drawn and sent annually only for those subjects with evidence of persistent engraftment of gene-modified T cells, or who test positive for RCL (Appendix 2, Table 3 Long-Term Follow-up, Years 6 through 15).

Persistence: PCR for the transgene vector sequence and/or flow cytometric analysis may be done on mononuclear cells to determine the persistence of CAR T cells. Absence of target cells may be considered a marker of functional persistence of the CAR T cells even in the absence of a positive PCR or flow cytometric test. The persistence assay will be discontinued after 2 successive negative tests. If the final time point(s) from active follow up are negative, they may be used for the documentation of successive negative tests.

Clonality: Subjects who, at any time point in long term follow up have a > 5% increase in cells positive for transgene expression, will have a repeat test within 1 month of result availability. If the percentage of cells positive for transgene expression continues to increase, additional testing for clonality will be performed. Clonality may be measured by either examining integration sites or TCR diversity among positive cells. If there is evidence of clonality, repeat testing will be performed no later than 3 months following evidence of clonality.

Replication-competent lentivirus (RCL): Evidence for RCL will be ascertained using VSVg qPCR at each time point during the first year. If all post-treatment assays are negative during the first year, then sample collection will be discontinued after year one. For those subjects with positive RCL testing at any time during the 1st year, further time points will be determined by sponsor after review with FDA.

9.5 Criteria for Removal from Active Follow-up

A subject may be discontinued from Active Follow-up at any time if the subject or the investigator feels that it is not in the subject's best interest to continue. Subjects who

discontinue Active Follow-up prior to Day 28 will enter Long-Term Follow-up. In the subset of subjects who are removed from active follow up prior to day +28, it is expected that adverse events and concomitant medications are still followed through day+28.

Subjects will be removed from active follow up for the following reasons:

- Subject completes Day 28 evaluations
- Subject/family is non-compliant with protocol procedures and/or clinic appointments
- Subject undergoes preparative chemotherapy for hematopoietic stem cell transplantation.
- Subject receives medical intervention prohibited under this protocol or which will interfere with the ability to assess toxicity or response following CAR T cell infusion. This includes initiation of any type of disease directed therapy.
- Subject meets criteria for removal from study

All subjects who have received a CAR T cell product on this protocol will be required to adhere to long-term follow-up adverse event and sample collection requirements for 15 years from the time of final CAR T cell product administration, as mandated by the FDA. Subjects who receive subsequent lentiviral gene modified cells will only be followed on this trial for survival and disease status (see Section 7.5.2).

9.6 Off-Study Criteria and Study Termination

All subjects are free to withdraw from participation at any time, for any reason, specified or unspecified, without prejudice. Reasonable attempts will be made by the investigator to provide a reason for subject withdrawals. The reason for the subject's withdrawal from the study will be recorded in the subject's source documents.

Subjects will be removed from the study for the following reasons:

- Subject, or subject's parents/legal guardian, withdraw consent for further participation
- Subject never received CAR T cell product
- 5 year anniversary of final CAR T cell infusion and enrolled onto a long-term follow-up protocol for gene therapy
- 15 year anniversary of final CAR T cell infusion
- Death
- Lost to follow-up

The study may be terminated at any time by the Sponsor or the FDA.

10 STATISTICAL CONSIDERATIONS

Prior to the analysis of the final study data, a detailed Statistical Analysis Plan (SAP) will be written describing all analyses that will be performed. The SAP will contain any modifications to the analysis plan described below.

10.1 Accrual and study duration

Up to approximately 18 evaluable subjects with B-ALL or NHL for Phase 1 will be required to assess the primary objective of evaluating safety and feasibility of treatment with SCRI-CAR22v2. Phase 2 will enroll up to 14 additional subjects with B-ALL (Phase 2 design of 20 evaluable subjects including the 6 subjects treated at the MTD/RP2D from Phase 1), to evaluate efficacy and gain additional safety data. The total number of subjects to enroll on the trial may be as high as 42, to account for an estimated 11% of subjects that will enroll but will not receive a CAR T cell infusion or who will be inevaluable for toxicity as well as included NHL subjects that may enroll but are not included as part of the phase 2 statistical design. The anticipated duration of the active treatment portion of the study is approximately 2 years.

10.2 Statistical Study Design

The primary goal of the study is to evaluate the toxicity and efficacy of SCRI-CAR22v2. The Phase 1 portion of the study will estimate the MTD and RP2D and both the Phase 1 and Phase 2 subjects will contribute to the toxicity evaluation. Efficacy will be defined by the CR, MRD negative response rate by Day 28 following infusion in B-ALL subjects. Both leukemia subjects who do not receive flu/cy lymphodepletion as well as those subjects with lymphomatous disease who receive SCRI-CAR22v2 will have responses evaluated descriptively.

Statistical analysis will entail descriptive statistics for which categorical variables will be summarized by number and percentage, and continuous variables will be summarized by mean, standard deviation, and range. Descriptive statistics will be summarized for each group singly and combined.

10.2.1 Phase 1 Statistical design

10.2.1.1 Rationale for the Proposed Design

Classical “3+3” dose escalation design is proposed to enroll at least 3 evaluable subjects at Dose Level 1. The objective is to determine the MTD as defined in Section 10.2.1.2. Definition of MTD. All subjects who receive SCRI-CAR22v2 and either experience a DLT or remain on active follow-up through Day 28, will be available for toxicity evaluation and contribute to the determination of the MTD. Adverse events will be graded using NCI CTCAE v5.0, except for protocol specific CRS and ICANS grading.

10.2.1.2 Definition of and determination of the MTD and BED

The maximum tolerated dose is defined as the T cell dose from among those tested for which DLT rate is closest to 20%, provided that it is also lower than 33% and that at least 6 subjects have been evaluated at that level. All observed DLT outcomes from toxicity-evaluable subjects will be tabulated by dose level. Per investigator discretion and with Data Monitoring Committee (DMC) approval, if no prescribed dose level reaches the MTD definition, the study will be suspended for review with DMC to determine whether additional dose levels should be added or other modifications to the protocol are necessary.

The biologically effective dose (BED) is the lowest dose with at least 6 subjects evaluable for both safety and efficacy, and having:

- A cumulative DLT rate under 33%;
- All 6 subjects are in remission with detectable CAR T-cells in the bone marrow at Day 28 evaluation.

The recommended Phase 2 dose (RP2D) will be either the MTD or the BED if the BED is lower than the MTD and the MTD is not determined.

10.2.1.3 Dose Escalation and De-escalation

1. Dosing will initiate at Dose Level 1
2. Subjects will be evaluated in cohorts of 3.
3. If there are no DLTs out of the first 3 subjects evaluated at a dose level, the dose level may increase.
    a. If no further dose escalation is permited based on no higher dose level availability, then an additional 3 subjects will be evaluated at the current dose level.
    b. If all three subjects are in remission with persistent CAR T cells in the bone marrow at Day 28 and without DLT, then the Study Chair may choose to not escalate to further evaluate the dose level for BED. In this case, if 3 additional patients confirm the current dose level to be a BED, the Study Chair may choose to stop dose escalation and proceed to Phase 2. Similarly, even if the dose level meets the definition of a BED, the Study Chair may opt to continue to explore higher dose levels if they are available.
4. If there is one DLT out of the first 3 subjects evaluated at a dose level, a second cohort of 3 subjects will be treated and evaluated at the current dose.
    a. If there is ≥ 1 DLT in the second cohort of 3 subjects (ie, there are ≥ 2 DLTs in the first 6 subjects), the current dose level will be shut down and dose assignment will de-escalate if a dose level below the currently evaluated dose level is available, to make sure there are at least 6 subjects evaluated at one level lower than the current dose.

b. If there are no DLTs in the second cohort of 3 subjects, the dose level may increase. If no further does escalation is permitted based on no higher dose level availability, or because of a DMC recommendation, then the current dose level would be considered the MTD/RP2D.
c. If there are no DLTs in the second cohort of 3 subjects, and all six subjects are in remission with persistent CAR T cells in the bone marrow at Day 28, then the study chair may choose to not escalate further as this dose level would meet the definition of a BED.

5. If 2-3 subjects out of the first 3 subjects evaluated at a dose level experience a DLT, the next cohort will de-escalate one dose level if a dose level below the current dose level is available, and the current dose level will be shut down. If the first 2 subjects both experience a DLT, and the 3rd subject has not received CAR T cells, the dose will de-escalate immediately by one dose level if available, and the 3rd subject will become the first subject of a new cohort.
6. If a subject, who has enrolled, is unable to wait for dose escalation, dose same, or de-escalation decision because of a waiting period of monitoring for DLT, they may proceed with treatment at the current dose level or one dose level below the current dose level, depending on the number of subjects currently awaiting DLT determination. In order to determine the dose level of the subject, it would need to be assumed that those awaiting DLT determination would be counted as having had a DLT. For example: If the first two subjects at current dose level had been treated and not experienced a DLT, and a third subject was awaiting DLT determination – then the subject could be treated at the current dose level. Otherwise, the subject would need to be treated at one dose level below the current dose level, e.g., if less than two subjects of a three-subject cohort had been treated at the current dose level without experiencing a DLT, then the subject would be treated at one dose level below. Subjects treated in this fashion would count towards a future cohort of three if their treated dose level was explored in a subsequent cohort.

10.2.1.4 Phase 1 Stopping Rules

During the phase 1 portion of the study, if either of the following occur, T cell infusions will be paused until a detailed review by the DMC has occurred. The DMC will recommend whether any further accrual should proceed.

- Any death that occurs in the absence of disease progression during active follow up.
- Occurrence of 2 or more grade 4 DLTs occurring in 2 study subjects
- The use of cetuximab in a subject with dosing intended to amerliorate a severe toxicity

10.2.2 Phase 2 Statistical design

The Simon's two-stage design (optimal) will be used for Phase 2 B-ALL subjects. At the end of stage one, if the number of subjects who demonstrate efficacy is fewer than planned, the trial will be suspended for review with the DMC to determine whether futility thresholds are met. If the number of subjects who have an efficacy response is more than planned for stage one, the trial will proceed through the completion of stage two. Please note that we may not have all subjects' response information after enrolling enough numbers for stage one, and the enrollment of new subjects and the administration of CAR T cell infusions for stage two will not be stopped during this period of uncertainty. Response assessment will be tracked by the Study Chair, co-investigators, and study statistician. A meeting with the DMC will be convened once adequate response data are available to assess stage one. Subjects from the Phase 1 portion who were treated at the RP2D will be included in the Phase 2 analysis.

The following assumptions underlie the Phase 2 two-stage design: At the end of the study, the efficacy will be ≥65%, against a null hypothesis of efficacy ≤35%. With this two-stage design, in the first stage 8 subjects will be treated (including subjects treated at the RP2D from Phase 1). If 3 or fewer respond among these 8 subjects, the study will be suspended. Otherwise, 12 additional subjects will be treated for a total of 20. The null hypothesis will be rejected if 10 or more efficacy responses are observed in 20 subjects. This design yields a one-sided type I error rate of 0.1 and a power of 0.87 when the true response is 65%.

Lymphoma subjects will be enrolled but there is no statistical design. It is anticipated that this group will be very small (likely to be less than 5 subjects). These subjects will be enrolled as necessary with descriptive analysis of persistence and efficacy.

10.2.3 Early stopping rules for toxicity

We will combine all subjects for safety evaluation, based on toxicity following subjects' infusion. As an additional safety assessment, an early safety review will occur after 12 subjects have been treated at the RP2D (including subjects treated at the RP2D during Phase 1). Additional infusions/treatment will be suspended pending review by a DMC, though enrollment and manufacturing may continue. The study will be paused if ≥ 33% of subjects within the first 12 have unacceptable toxicities as described in Section 10.2.3.1 Unacceptable Toxicities for Phase 2.

Operationally, T cell infusions will be temporarily suspended and the study will be referred to the DMC for consideration of results and appropriate modification or termination of the study if:

- The treatment of additional subjects will be suspended if 4 out of the first ≤ 12 subjects (including 6 subjects treated at the RP2D from Phase 1) have

unacceptable toxicity as per Section 10.2.3.1 Unacceptable Toxicities for Phase 2 that are attributed to CAR T cells.

- There ever exists sufficient evidence to suggest that a death is possibly, probably or definitely due to CAR T cell infusion, further T cell infusions will be suspended pending a detailed review by the DMC

If the true probability of having unacceptable toxicity per Section 10.2.3.1 Unacceptable Toxicities for Phase 2 is 5%, the probability of suspension due to AEs after 12 subjects is approximately <0.01. If the true probability of having unacceptable toxicity or AEs is 50%, the probability of suspension due to AE is approximately 0.93 (probabilities of suspension is estimated from 5,000 simulations).

If the early stopping rule is activated, the treatment of additional subjects will be paused and the data reviewed to determine if the results can be explained by the patient population (e.g. older, more comorbidities) or by the toxicity of the regimen. Once the trial is suspended, the nature of events leading to stopping will be assessed by the Study Chair. The DMC will recommend whether any further accrual should proceed.

The toxicities observed will be summarized in terms of type (organ affected or laboratory determination such as absolute neutrophil count), severity (by NCI CTCAE version 5), date of onset and attribution. Tables will be created to summarize these toxicities by each group and combined.

10.2.3.1 Unacceptable Toxicities for Phase 2

Subjects who experience an adverse event listed below, which is attributed as probably or definitely related to their initial CAR T cell infusion on this protocol, will be included as an unacceptable toxicity in the early stopping safety analysis for Phase 2:

- Grade 5 AE
- Medically significant Grade ≥ 4 AE lasting > 72 hours
- Medically significant Grade ≥ 3 AE lasting > 2 weeks
- Medically significant Grade ≥ 3 neurotoxicity > 72 hours

10.3 Evaluability Definitions:

10.3.1 Toxicity

If a subject is removed from study prior to receiving the initial CAR T cell infusion, they will be replaced.

10.3.2 Dose Limiting Toxicity

Only subjects with leukemia will be evaluable for dose limiting toxicity. Subjects will be evaluable for the occurrence of a dose limiting toxicity if they receive a SCRI-CAR22v2 infusion during phase 1 and either:

- Experiences a DLT prior to removal from active follow up
- Receive lymphodepletion with fludarabine/cyclophosphamide and remains in active follow up through Day +28 without a DLT

Phase 1 subjects who are not evaluable for DLT will be replaced.

10.3.3 Biologically Effective Dose

All subjects who receive SCRI-CAR22v2 and are evaluable for response and DLT will be included in the analysis of the BED.

10.3.4 Feasibility

All subjects who undergo apheresis or provide a previously obtained acceptable apheresis product will be included in the feasibility analysis.

10.3.5 Disease Response

A subject will be considered evaluable for disease response if:

- the subject meets the eligibility criteria for pre-infusion criteria;
- the subject receives the CAR T cell infusion; and
- the subject is under follow-up for a sufficient period to evaluate the disease and meets criteria for having evaluable disease.
- Response will be characterized using Day 28 disease evaluations. A subject who dies because of toxicity related to the investigational CAR T cell product and prior to undergoing a disease response evaluation will be considered a non-responder.

Phase 2 subjects who are not evaluable for disease response will be replaced.

10.4 Endpoint Definitions

10.4.1 Toxicity

Toxicity will be determined by defining Adverse Events occurring after infusion of CAR T cell product. The Adverse Events observed will be summarized in terms of type (organ affected or laboratory determination such as absolute neutrophil count), severity (by NCI CTCAE version 5), date of onset and attribution. Tables will be created to summarize these toxicities by each group and combined.

10.4.2 Feasibility

Feasibility will be determined by the rate of manufacturing a CAR T cell product from apheresis product that is able to be released for infusion.

10.4.3 Leukemia Relapse

All relapses will be classified as CD22+ or CD22 negative as well as CD19+ or CD19 negative.

Bone Marrow Relapse is defined as M2 marrow after previous remission from ALL.

MRD relapse is defined as an increase in MRD level of at least 1 log.

CNS Relapse is defined as:

- At least 5 WBC's/µL in CSF with blasts present on cytospin

or

- Any number of WBC's in CSF with immunophenotypic proof of leukemic relapse. Immunophenotypic proof of relapse is defined as identifiable blasts **plus** (for B-lineage) TdT or CD10 positivity on 2 consecutive CSF samples four weeks apart **or** (for T-lineage) TdT and CD7 or TdT positivity alone on 2 consecutive CSF samples four weeks apart.

Testicular Relapse is defined as: Unilateral or bilateral testiculomegaly with biopsy-proven testicular involvement (unless part of a combined relapse, in which case testiculomegaly or abnormal imaging is sufficient for the testicular relapse component).

Non-CNS, Non-testicular Isolated Extramedullary Relapse is defined as new or recurrent disease in a site excluding bone marrow, CNS or testicular disease.

Combined Relapse is defined as relapse at 2 or more of the above sites.

10.4.4 Lymphoma Relapse

Appearance of new lesions, appearance or reappearance of tumor cells in bone marrow or CSF. All relapses will be classified as CD22+ or CD22 negative as well as CD19+ or CD19 negative.

10.4.5 CD22+ B cell aplasia

BCA is defined as <1% of lymphocytes expressing CD22. Survival of BCA is defined from the time of CAR T cell infusion to recovery of B cells for the subset of subjects who achieve BCA following CAR T cell infusion. Subjects who receive HCT in a state of BCA or discontinue protocol therapy in a state of BCA are censored at the time of their most recent evaluation.

10.4.6 Persistence of SCRI-CAR22v2

Defined as either detection of the CAR+ T cells by flow or PCR above the lower limit of detection, or B cell aplasia that cannot be attributed to other B cell targeting agents.

10.4.7 Overall Survival

Time from CAR T cell infusion to death from any cause. If a subject is alive at the last evaluation time period, survival time is censored at the time of last follow-up.

10.4.8 Disease Free Survival

Calculated for the subset of subjects who attained an MRD negative CR (leukemia) or a CR (lymphoma) per Appendix 6: and Appendix 7: respectively, after CAR T cell infusion; defined as time from CAR T cell infusion to the first observation of disease recurrence or death from any cause, whichever occurs first. If the subject has not relapsed or died, disease-free survival is censored at the time of last follow-up.

10.4.9 Non-Relapse Mortality

Time to death where cause of death is not attributable to underlying disease. Relapse and progression, including death attributable to underlying disease, are treated as competing risks for NRM and censored at time of last follow-up for those who do not relapse, progress or die.

10.4.10 Event Free Survival

Time from CAR T cell infusion to an event, with events defined as not having achieved remission (MRD negative CR for leukemia or CR for lymphoma) by Day 28, relapse after achieving initial remission after CAR T cells, secondary malignancy, or death from any cause.

10.5 Safety Monitoring

10.5.1 Weekly Safety Review

The Study Chair, Investigators, study statistician (if needed), study coordinator and relevant site staff will meet weekly (or as needed when there are active subjects) to review subject enrollment and conduct subject safety review. This group is responsible for monitoring the data and safety of this study, including implementation of the stopping rules. During the meeting, the group will review as applicable enrollment, AEs, and protocol compliance, CAR T cell persistence analysis, feasibility data and follow-up information for each subject.

10.5.2 Data Monitoring Committee

The study will be monitored by a Data Monitoring Committee (DMC). This is an independent committee with no affiliation to the protocol. The DMC will meet prior to the study opening to review and approve the study protocol and DMC Charter. The DMC will review toxicity data approximately every 6 months. In addition, the DMC will review study conduct including accrual, drop-outs, data completeness, any inability to generate T cell

product that meets all Quality Control criteria, positive bacterial cultures from the T cell product, subjects not meeting eligibility criteria for CAR T cell infusion after enrollment, protocol compliance, and treatment efficacy measures.

DMC meetings may be called at any time by the DMC chair or Sponsor for additional safety review if indicated. Following any temporary suspension of accrual for a safety event, the DMC will be convened and will further review the safety data to determine if continuation of accrual is appropriate. Applicable regulatory agencies will receive copies of the DMC's recommendations as they become available.

11 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

11.1 Definition of Adverse Event (AE)

According to 21 CFR 312.32(a): "An adverse event is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related." An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of an investigational product, whether or not related to the investigational products. AEs may also include pre- or post-treatment complications that occur as a result of protocol specified procedures, lack of efficacy, overdose, drug abuse/misuse reports, or occupational exposure. Pre-existing events that increase in severity or change in nature during or as a consequence of participation in the clinical study will also be considered AEs.
An AE does not include the following:

- Medical or surgical procedures such as surgery, endoscopy, tooth extraction, and transfusion. The condition that led to the procedure may be an adverse event and must be reported.
- Pre-existing diseases, conditions, or laboratory abnormalities present or detected before the infusion of investigational product that do not worsen.
- Situations where an untoward medical occurrence has not occurred (e.g., hospitalization for elective surgery, social and/or convenience admissions).
- Overdose without clinical sequelae.
- Any medical condition or clinically significant laboratory abnormality with an onset date before infusion of investigational product and not related to a protocol-associated procedure is not an AE. It is considered to be pre-existing and should be documented on the medical history CRF.

A suspected adverse reaction is any AE for which there is a reasonable possibility that the investigational product caused the AE. For the purposes of expedited safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the investigational product and the AE. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by an investigational product.

Life-threatening AE or life-threatening suspected adverse reaction is an AE or suspected adverse reaction that, in the view of either the investigator or study Sponsor, places the subject at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

11.2 Definition of Serious Adverse Event (SAE)

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or the study Sponsor, it results in any of the following outcomes:

- Death of any cause
- A life-threatening AE
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- A secondary malignancy

Important medical events that may not result in death, be immediately life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

11.3 Classification of Adverse Events

11.3.1 Grading of Adverse Events

Wherever possible, the severity of AEs other than CRS and Immune Effector Cell-Associated Neurotoxicty Syndrome (ICANS) will be graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE version 5). Grading of CRS and ICANS will occur according to CRS and ICANS grading scale noted in the tables below.

Table 11-1 CRS Grading[1]

Grade	Description of Symptoms
1: Mild	Not life-threatening, require only symptomatic treatment such as antipyretics and anti-emetics (e.g., fever [2] ≥ 38.0°C, nausea, emesis, fatigue, headache, myalgia, malaise)
2: Moderate	Require and respond to moderate intervention: • Oxygen requirement for low flow nasal cannula [3] or blow by oxygen, or • Hypotension responsive to fluids
3: Severe	Require and respond to aggressive intervention: • Oxygen requirement for high flow nasal canula, facemask, non-rebreather or Venturi mask, and/ or • Hypotension requiring a one vasopressor with or without vasopressin
4:Life-threatening	Life-threatening: • Requirement for positive pressure support including ventilator support, CPAP or BiPAP • Hypotension requiring multiple vasopressors (excluding vasopressin)
5: Fatal	Death

[1] CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a patient with temperature of 39.5°C, hypotension requiring one vasopressor and hypoxia requiring low-flow nasal cannula is classified as having Grade 3 CRS. Organ toxicities associated with CRS may be graded according to CTCAE v5.0 but they do not influence CRS grading.

[2] Fever is defined as temperature ≥38.0°C not attributable to any other cause. In patients who have CRS then receive antipyretics or anti-cytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.

[3] Low-flow nasal cannula is defined as oxygen delivered at ≤ 6 liters/minute. Low flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula is defined as oxygen delivered at > 6 liters/minute

Table 11-2 Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) Grading[1]

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score (children >12 years [2])	7-9	3-6	0-2	0 (patient is unarousable and unable to perform ICE)
CAPD score (children ≤12 years)	<9	<9	≥9	Unable to perform CAPD
Depressed level of consciousness [3]	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma
Seizure (any age)	N/A	N/A	Any clinical seizure focal or generalized that resolves rapidly; or Non-convulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (>5 min); or Repetitive clinical or electrical seizures without return to baseline in between.
Motor weakness [4] (any age)	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis
Raised ICP / Cerebral Edema (any age)			Focal/local edema on neuroimaging [5]	Decerebrate or decorticate posturing; or Cranial nerve VI palsy; or Papilledema; or Cushing's triad; or Signs of diffuse cerebral edema on neuroimaging

Refer to Appendix 8: for ICE and CAPD scoring systems. ICE: Immune effector Cell-associated Encephalopathy; CAPD: Cornell Assessment of Pediatric Delirium; ICP: Intracranial pressure; EEG: electroencephalogram.

[1] ICANS grade is determined by the most severe event (ICE or CAPD score, level of consciousness, seizure, motor findings, raised ICP/cerebral edema) not attributable to any other cause.

[2] A patient with an ICE score of 0 may be classified as having Grade 3 ICANS if the patient is awake with global aphasia. But a patient with an ICE score of 0 may be classified as having Grade 4 ICANS if the patient is unarousable.

[3] Depressed level of consciousness should be attributable to no other cause (e.g. no sedating medication)

[4] Tremors and myoclonus associated with immune effector cell therapies may be graded according to CTCAE v5.0 but they do not influence ICANS grading.

[5] Intracranial hemorrhage with or without associated edema is not considered a neurotoxicity feature and is excluded from ICANS grading. It may be graded according to CTCAE v5.0.

If an AE cannot be graded using the NCI CTCAE criteria or the study-specific CRS grading scale, it should be graded as mild, moderate, severe, life-threatening, or death using the following definitions.

Mild (Grade 1): Awareness of signs or symptoms, but easily tolerated and of a minor irritant type, causing no loss of time from normal activities. Symptoms do not require therapy or a medical evaluation; signs and symptoms are transient.
Moderate (Grade 2): Events introduce a low level of inconvenience or concern to the subject and may interfere with daily activities, but are usually improved by simple therapeutic measures; moderate experiences may cause some interference with functioning.
Severe (Grade 3): Events interrupt the subject's normal daily activities and generally require systemic drug therapy or other treatment; they are usually incapacitating.
Life-threatening (Grade 4): Events that place the subject at immediate risk of death or are disabling.
Death (Grade 5): Events that result in death.

To make sure there is no confusion or misunderstanding of the difference between the terms "serious" and "severe," which are not synonymous, the following note of clarification is provided. The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious" which is based on subject/event outcome or action criteria usually associated with events that pose a threat to a subject's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

11.3.2 Relationship of Adverse Event to Treatment

The investigator will assess the potential relationship of the AE to investigational product using the following descriptions.

Related: This category applies to an AE that is clearly not related to the investigational agent/procedure, beyond a reasonable doubt. That is, another cause of the event is most plausible; and/or a clinically plausible temporal sequence is inconsistent with the onset of the event and the exposure to study drug and/or a causal relationship is considered biologically implausible.
Unlikely Related: This category applies to an AE that is doubtfully related to the investigational agent/procedure. That is, another cause of the event is highly likely; and/or there is not a reasonable temporal sequence from administration of the study drug or one that follows a known or expected response pattern to the suspected study drug. The event could readily have been produced by a number of other factors.
Possibly Related: This category applies to an AE that may be related to the investigational agent/procedure. That is, the AE follows a reasonable temporal sequence from administration of the study drug and that follows a known or expected response pattern to the suspected study drug, but that could readily have been produced by a number of other factors.
Probably Related: This category applies to an AE that is likely related to the investigational agent/procedure. That is, the AE has a temporal relationship to the administration of the

investigational agent(s) or research intervention and follows a known or suspected pattern of response.
Definitely Related: This category applies to an AE that is clearly related to the investigational agent/procedure. That is, the AE has a temporal relationship to the administration of the investigational agent(s) or research intervention and follows a known or suspected pattern of response.

11.4 Expectedness, Pre-Existing Conditions, and Persistent Adverse Events

Expectedness: The study Sponsor will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the investigational product.
Pre-Existing Conditions: If a pre-existing condition worsens in severity, the worsening may require reporting as an AE or SAE. In addition, if a condition present at baseline resolves and then recurs, the reoccurrence may require reporting as an AE or SAE.
Persistent Adverse Events: A persistent AE is one that extends continuously, without resolution. A persistent AE is reported only once unless the grade and/or frequency become more severe. If the grade becomes more severe the original AE will be considered to have stopped on the date the severity increased and the AE must be reported again with the higher grade and/or frequency.

11.5 Serious Adverse Event Reporting

SAEs occurring from the beginning of the infusion of the investigational product up to and including 30 days following the infusion of the investigational product will be evaluated by the PI or sub-investigator and must be reported in the eCRF and to the Sponsor according to the guidelines below. Written notification of SAEs must be reported to the study Sponsor or its designee within 24 hours of the investigator becoming aware of the event (see Section 11.5.1 Study-specific SAE reporting). SAEs occurring after 30 days following the last treatment with the investigational product, which, in the judgement of the investigator or treating physician, are ***possibly, probably*** or ***definitely*** related to treatment with the investigational product, will be reported to the study Sponsor or its designee within 24 hours of the investigator becoming aware of the event.

Initial SAE reports must be followed by detailed descriptions. These should include copies of hospital case records and other documents when requested. Telephone reports must be confirmed promptly by written report.

Additionally, the Investigator is responsible for submitting follow-up reports for all SAEs until the SAE has resolved or until the subject's condition stabilizes (in case of persistent impairment), or the study subject dies.

11.5.1 Study-specific SAE reporting

Planned hospitalization will not be reported to the Sponsor as an SAE. Planned hospitalizations may include admission for:

- elective treatment of a pre-existing condition
- routine monitoring of the subject not associated with any deterioration in condition
- monitoring following CAR T cell infusion if minor (non-serious) symptoms indicate the potential for more significant medical problems

The following toxicities, if meeting the definition of an SAE, will be entered into the eCFR but do not require a written report to the Sponsor:

- Grade 1- 4 anemia, decrease in lymphocytes, neutrophils/granulocytes (ANC/AGC) or platelet count, with or without hospitalization
- Grade 1 fever
- Grade 3 febrile neutropenia
- Grade 3 catheter-related infection with or without hospitalization

11.6 IND Safety Reporting

This study will comply with Title 21 of the Code of Federal Regulations (CFR), Section 312.32, which requires that the sponsor notify the FDA and participating investigators in an IND Safety Report of potentially serious risks from clinical trials or any other source. Reports must be submitted no later than 15 calendar days after the Sponsor becomes aware of the information and determines it is reportable.
The Sponsor will submit an IND Safety Report for individual events meeting the following criteria:

- There is a reasonable probability the drug under study caused the event (ie, there is evidence to suggest a causal relationship between the drug and the AE).
- The event meets the criteria in Section 11.2 Definition of Serious Adverse Event for a serious adverse event and does not meet the criteria in Section 11.5.1 Study-specific SAE reporting.
- The event is unexpected (ie, it is not consistent with the risk information in the protocol or other information submitted to the FDA in the IND)

Analysis of 1 or more occurrences of the same event, and/or aggregate analysis of specific events, may lead the Sponsor to determine that information requires reporting via an IND Safety Report.

11.7 Reporting of Pregnancy

In subjects who have ongoing persistence of the CAR T cells, pregnancies in subjects or partners must be reported within 24 hours of knowledge of the event to the study Sponsor or

its designee. The investigator must make every effort to follow the pregnancy of either the subject or partner through resolution of the pregnancy (delivery or termination) and report the resolution to the study sponsor or its designee. In the event of a pregnancy in the partner of a subject, the investigator should make every effort to obtain the female partner's consent for release of protected health information.

11.8 Safety Reporting

An SAE report form will be provided by the Sponsor to sites for the Investigator or designee to use in reporting SAEs to the Sponsor.

12 ADMINISTRATIVE, ETHICAL, AND REGULATORY CONSIDERATIONS

Coordinating center responsibilities will be undertaken by the Clinical Development Team at Seattle Children's Therapeutics.

12.1 Good Clinical Practice

This protocol is written in accordance with the principles established by the 18th World Medical Assembly General Assembly (Helsinki, 1964) and subsequent amendments and clarifications adopted by the General Assemblies. The investigator will make every effort that the study described in this protocol is conducted in full conformance with those principles, current FDA regulations, ICH Good Clinical Practices (GCP) guidelines, and local ethical and regulatory requirements. Should a conflict arise, the investigator will follow whichever law or guideline affords the greater protection to the individual subject. The investigator will also make sure he or she is thoroughly familiar with the appropriate administration and potential risks of administration of the study drug, as described in this protocol, prior to the initiation of the study.

12.2 Institutional Review Boards (IRB) and Institutional Biosafety Committees (IBC)

The protocol and consent form, and any accompanying material to be provided to subjects, will be reviewed and approved by the institutional Review Board/Institutional Ethics Committee (IRB/IEC) and/or Institutional Biosafety Committee (IBC) of the participating center prior to study initiation. Serious adverse experiences regardless of causality will be reported to the IRB/IEC and/or IBC in accordance with the standard operating procedures and policies of the IRB/IEC and/or IBC, and the Investigator will keep the IRB/IEC and/or IBC informed as to the progress of the study. The Investigator will obtain assurance of IRB/IEC compliance with regulations.

Any documents that the IRB/IEC and/or IBC may need to fulfill its responsibilities (such as protocol, protocol amendments, Investigator's Brochure (IB), consent forms, information concerning subject recruitment, payment or compensation procedures, or other pertinent information) will be submitted to the IRB/IEC and/or IBC. The IRB/IEC's and/or IBC's written unconditional approval of the study protocol and the informed consent form will be in the possession of the Investigator before the study is initiated.
Before implementation, the investigator will submit to and receive documented approval from the IRB/IEC for any modifications made to the protocol or any accompanying material to be provided to subjects after initial IRB/IEC approval, with the exception of those necessary to reduce immediate risk to study subjects.

The IRB/IEC must be informed of revisions to other documents originally submitted for review; serious and/or unexpected adverse experiences occurring during the study in

accordance with the standard operating procedures and policies of the IRB/IEC; new information that may affect adversely the safety of the subjects of the conduct of the study; an annual update and/or request for re-approval; and when the study has been completed. Research modifications will be submitted to the IBC according to NIH guidelines, standard operating procedures and policies of the IBC.

12.3 Informed Consent/Assent and Other Informational Documents Provided to Study Subjects

The Investigator will prepare the informed consent form, assent and the Health Insurance Portability and Accountability Act (HIPAA) authorization and provide the documents to the Sponsor or its designee for approval prior to submission to the IRB/IEC. The consent/assent form generated by the Investigator must be acceptable to the Sponsor and be approved by the IRB. The written consent documents will comply with the elements of informed consent as described in 21 CFR Part 50 and ICH E6, and will also comply with local regulations. The Investigator will send a copy of the IRB-approved Informed Consent/Assent Form to the Sponsor or its designee for the study file.

A properly executed, written, informed consent will be obtained from each subject prior to entering the subject into the trial. Information should be given in both oral and written form and subjects or their legal representatives must be given ample opportunity to inquire about details of the study. If appropriate and required by the local IRB, assent from the subject will also be obtained. If a subject is unable to sign the informed consent form (ICF) and the HIPAA authorization, a legal representative may sign for the subject. A copy of the signed consent form (and assent) will be given to the subject or their legal representative and will be provided any new information during the course of the study that might affect their continued participation in the study.

If the protocol is amended and the ICF (and assent, if applicable) is revised, each subject or their legal representative will be required to provide written informed consent/assent again using the revised ICF (and assent, if applicable).

Receipt of written informed consent/assent will be documented in each potential subject's CRF. The signed ICF will remain in each subject's study file and must be available to the study monitor(s) at all times.

13 DATA HANDLING AND RECORD KEEPING

13.1 Case Report Forms and Source Documents

The investigator is required to initiate and maintain, for each subject, an adequate and accurate case history that records all observations and other data related to the study for that subject. A validated electronic data capture system will be used for entry of the data into electronic Case Report Forms (CRFs). Data must be recorded on CRFs approved by the Sponsor or its designee. All information recorded on CRFs for this study must be consistent with the subject's source documentation.

Initial data entry and any changes to the data will be made only by SCRI-authorized users, and data entries and changes will be captured in an electronic audit trail. An explanation of any data change should be recorded in the CRF. All data entered in to the CRF must be verifiable; therefore, CRFs will be routinely checked for accuracy, completeness, and clarity and will be cross-checked for consistency with source documents, including laboratory test reports and other subject records by the Sponsor or its designee. The investigator must allow direct access to all source documents.

13.1.1 Data Quality Assurance

Quality assurance will be monitored by the sponsor/sponsor designee at a minimum of twice per year. The sponsor may delegate monitoring responsibilities to an external vendor. Monitoring visits occur at specified intervals determined by the assessed risk level of the study and the findings of previous visits.

The trial will comply with the standard guidelines set forth by these regulatory committees and other institutional, state and federal guidelines.

The investigator understands that regulatory authorities, the IRB/IEC, and/or SCRI or its designees have the right to access all CRFs, source documents, and other study documentation for on-site audit or inspection and will retain this right from the start of the study to at least two years after the last approval of a marketing application or for at least two years after clinical development of the study drug for the indication being studied has been discontinued. The investigator is required to guaranty access to these documents and to cooperate with and support such audits and inspections.

13.1.2 Record Retention

All study records must be retained for at least two years after the last approval of a marketing application in the US or an ICH region and until: 1) there are no pending or contemplated marketing applications in the US or an ICH region or 2) at least two years have elapsed since the formal discontinuation of clinical development of the investigational product under study. The investigator/institution should retain subject identifiers for at least 15 years after the completion or discontinuation of the study. Subject files and other source data must be kept

for the maximum period of time permitted by the hospital, institution or private practice, but not less than 15 years. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an SCRI agreement. SCRI must be notified and will assist with retention should the investigator/institution be unable to continue maintenance of subject files for the full 15 years. All study records must be stored in a secure and safe facility.

13.2 Investigational Product Accountability

While at the clinical site, investigational product must be stored in a secure limited access location at controlled temperature as required and according to product packaging. The storage facility must be available for inspection by the study monitor at any time during the study. A drug accountability record must be maintained for all investigational product received, dispensed, returned, and/or lost during the study. This record must be kept current and made available to the study monitor for inspection.

13.3 Protocol Deviations

A protocol *deviation* is any change, divergence, or departure from the study design or procedures defined in the protocol. In general, protocol deviations are classified as either *Major* (or "*important*" per ICH E3 Structure and Content of Clinical Study Reports — Questions and Answers R1) or *Minor*.
Major or important protocol deviations are a subset of protocol deviations that might significantly affect the completeness, accuracy, and/or reliability of the study data or that might significantly affect a subject's rights, safety, or well-being. For example, *major* or *important protocol deviations* might include enrolling subjects in violation of key eligibility criteria or failing to collect data necessary to interpret primary objectives, as this may compromise the scientific value of the trial.
Minor protocol deviations are protocol deviations that do not have a substantive effect on the subject's rights, safety, or well-being or the integrity of the data. For example, *minor protocol deviations* might include a missed study visit "window."

Major or important protocol deviations or this study include, but are not limited to, the following reasons:

- Failure to meet inclusion/exclusion criteria
- Use of a prohibited concomitant medication
- Failure to comply with Good Clinical Practice (GCP) guidelines.

The Investigator will determine if a *major* or *important protocol deviation* will result in withdrawal of a subject. All deviations will be reported to the Sponsor and the IRB/IBC in accordance with reporting requirements.

13.4 Subject-Specific Biological Materials

At the completion of the study unused CAR T cell product, and biological samples including serum, CSF and cryopreserved PBMC samples, will become property of the Sponsor and may be used in non-therapeutic experiments.

13.5 Investigator's Responsibilities

By signing this protocol (Appendix 1:), the Principal Investigator agrees to:

- Conduct the study in accordance with the protocol and only make changes after notifying the Sponsor (or designee), except when to protect the safety, rights or welfare of subjects.
- Personally conduct or supervise the study (or investigation).
- Ensure that the requirements relating to obtaining informed consent and IRB/IEC review and approval meet federal guidelines, as stated in 21CFR parts 50 and 56.
- Report to the Sponsor or designee any AEs that occur in the course of the study, in accordance with 21 CFR 312.64.
- Ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments.
- Maintain adequate and accurate records in accordance with 21 CFR 312.62 and to make those records available for inspection with the Sponsor or its designee.
- Ensure that an IRB/IEC that complies with the requirements of 21 CFR 56 will be responsible for initial and continuing review and approval of the clinical study.
- Promptly report to the IRB/IEC and the Sponsor or its designee all changes in the research activity and all unanticipated problems involving risks to subjects or others (to include amendments and IND safety reports).
- Ensure IRB/IEC approval before any changes are made in the research study, except when necessary to eliminate immediate hazards to the subjects.
- Comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements listed in 21 CFR 312.

13.6 Publication Policy

The publication or presentation of any study results shall comply with all applicable privacy laws, including, but not limited to, HIPAA. Material must be reviewed and approved by the Sponsor prior to submission for publication.

13.7 Financing and Insurance

Financing and insurance for this clinical trial will be addressed in clinical trial agreements with the study site as applicable.

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APPENDIX 1: SIGNATURE PAGE

Protocol Title: Pediatric and Young Adult Leukemia Adoptive Therapy (PLAT)-07: A Phase 1/2 Study Of CD22-Specific CAR T Cells For CD22+ Leukemia Or Lymphoma

Protocol Number: PLAT-07

Sponsor Acknowledgement:

As the Sponsor representative, I confirm that SCTx will comply with all Sponsor obligations as detailed in all applicable regulations and guidelines. I will ensure that the investigator is informed of all relevant information that becomes available during the conduct of this study.

DocuSigned by:
Rebecca Gardner
Signer Name: Rebecca Gardner
Signing Reason: I approve this document
Signing Time: 7/7/2022 | 3:22:33 PM PDT
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7/7/2022 | 3:22:37 PM PDT

Rebecca Gardner, MD — Date

Medical Director, Seattle Children's Therapeutics

Principal Investigator Acknowledgement:

I have read Protocol, including all appendices, and I agree to conduct the study as detailed in this protocol and in compliance with the Declaration of Helsinki, Good Clinical Practices (GCP) and all applicable regulatory requirements and guidelines.

Principal Investigator	Date

APPENDIX 2: SCHEDULE OF PROCEDURES

Appendix 2, Table 1 CAR T Cell Infusion: Screening through Day 28

Time Point:	Screening	Evaluation / Pre-apheresis	Apheresis	Pre-lymphodepletion*	Pre- T cell infusion	SCRI-CAR22v2 infusion	Day						
							1	3	7	10	14	21	28
Procedure Window	a	b	b	b	b	b	c	c	c	c	c	c	c
Eligibility determination	X	X			X								
Demography	X												
Performance status [1]	X												
PE & VS [2]	X	X		X	X		X		X	X	X	X	X
Neurologic exam					X				X		X	X	
GVHD assessment	X				X				X		X	X	X
Echocardiogram	X[d]				X [3]								
Pregnancy test [4]	X												
Pulse oximetry	X	X			X								
Chemistry [5]	X			X	X		X		X	X	X	X	X
Hematology [6]	X	X		X	X		X	X	X	X	X	X	X
Serum IgG					X								X
Inflammatory markers [7]					X				X	X	X	X	X
Virology [8]	X[e]												
CSF [9]	X[d]			X						X			X
Correlative Studies Peripheral Blood [10]		X			X		X	X	X	X	X	X	X
Correlative Studies – Other													
Bone marrow unilateral aspirate [11]	X[d]			X						X			X
PET scan [12]				X									X
CT scan [13]				X									X
Apheresis			X										
SCRI-CAR22v2 infusion						X							
Concomitant medications			X				*Continuous through Day 30*						
Active Medical Conditions	X				X								
Adverse events[14]						*Continuous from infusion through Day 30; related SAE ongoing*							
CRS labs [15]							*Daily when Grade 2-4 CRS is occurring*						

* if lymphodepletion is not needed (per Section 8.4) still required to undergo disease restaging with CSF, bone marrow aspirate, PET scan (if applicable) and CT scan (if applicable). Disease restaging evaluations window is within 14 days prior to CAR T cell infusion if subject is not undergoing lymphodepletion.

a Must be obtained within 7 days prior to enrollment unless otherwise noted. Evaluations that were performed as part of standard care within window do not need to be repeated.

b Evaluation before apheresis, lymphodepletion and CAR T cell infusion must be performed within 2 days prior to timepoint EXCEPT: See footnote 3 below.

c Evaluations must be performed within +/- 3 days of time point

d May be obtained up to 14 days prior to enrollment

e May be obtained up to 3 months prior to enrollment

1 Lansky (patients <16 years of age) or Karnofsky (patients ≥ 16 years of age) (See Appendix 3)

2 Height and body surface area are obtained at Screening and prior to CAR T cell infusion;

3 ECHO should only be repeated if the subject has received anthracyclines following enrollment or had an ECHO performed after enrollment demonstrating EF of <50% or SF<28%; ECHO may be obtained up to 14 days prior to T cell infusion.

4 Females of child-bearing potential

5 Serum sodium, potassium, chloride, bicarbonate, BUN/urea, creatinine, total and conjugated bilirubin, alanine aminotransferase (ALT), LDH, uric acid, calcium, magnesium, phosphorus

6 Complete blood count (CBC), differential and platelet count

7 Ferritin and CRP

8 HIV antigen & antibody, hepatitis B surface antigen, and Hepatitis C antibody. Hepatitis C PCR if Hepatitis C antibody is positive.

9 CSF cell count and cytology on all specimens. Glucose and protein are required on all but screening specimen. Up to 3mL of CSF will be collected at pre-lymphodepletion and on Day 10 and 28 and sent to CSL for correlative studies. In the event of ≥ Grade 2 CNS toxicity, CSF should be obtained and; if available, an additional up to 3mL may be collected and sent to CSL for correlative studies. See Lab Manual for full details

10 Refer to study-specific lab manual for requirements for all correlative studies samples. Up to 1mL/kg (not to exceed 40mL) to CSL for correlative studies. RCL testing will be performed on the Pre-T cell infusion sample as the baseline sample. If testing is not successful, the pre-apheresis sample will be tested as the baseline.

11 Standard morphology and multiparameter flow cytometry for minimal residual disease (MRD) required for each marrow. Cytogenetics must be done on a marrow pre-enrollment; can be done at any time over the course of the current relapse and does not need to be repeated for the study. An additional up to 5 mL will be collected at pre-lymphodepletion, Day 10 and Day 28 evaluations and sent to CSL for correlative studies. Refer to study specific lab manual for requirements of all correlative studies samples.

12 Required if last PET was positive for active disease in leukemia subjects with known extramedullary, non-CNS, non-testicular disease involvement, and required for all lymphoma subjects.

13 Required for lymphoma subjects; sites clinically indicated for subject's disease

14 Record information on hospitalization, ICU admission, and ANC recovery following CAR T cell infusion

15. CRS labs include CRP, LDH, ferritin, D-Dimer, PT, PTT, fibrinogen, and absolute lymphocyte count.

Appendix 2, Table 2 Long-Term Follow-Up, Years 1 through 5

Time Point *(months following most recent CAR T-cell infusion)*:	2	3	4* 5*	6	7*, 8* 9*, 10* 11*	12	15*	18*	24	30*	36	42*	48	54*	60
Procedure Window	a	a	a	a	a	b	b	b	b	b	b	b	b	b	b
Medical history [1,2]				X		X			X		X		X		X
PE [1]				X		X			X		X		X		X
CAR T cell Persistence [3, 4]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
RCL [3, 5]		X		X		X									
Serum IgG [6]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Immune reconstitution [3]				X											
Delayed Related AEs of interest [7]	*Continuous*														

* Required only if subject had ongoing CAR T cell persistence at last check or required for confirmation of loss of persistence. For subjects who have a CD22 negative recurrence or undergo an allogeneic HCT, samples are required at 6 month intervals rather than monthly and should be drawn in conjunction with required RCL time points when possible.

a Evaluations must be performed within +/- 1 month of time point

b Evaluations must be performed within +/- 2 months of time point

1 May be performed by local physician or treating oncologist

2 Medical events relevant to subject's disease and treatment, inclusive of infectious disease and use of immunoglobulin replacement. If relevant, records pertaining to disease response and/or relapse will be collected.

3 Up to 15 mL peripheral blood to CSL, see Lab Manual for full details.

4 Persistence testing will be discontinued after 2 successive negative results, including tests from the final timepoint(s) of the active treatment phase. Optional time points include months 2, 3, 4, 5, 7, 8, 9 10, and 11 to be obtained if labs at that timepoint are clinically indicated.

5 See Section 9.4 Post-Treatment Long-Term Follow-Up for details. Further timepoints will be determined by sponsor after review with FDA if RCL testing is positive at any of the timepoints during the 1st year.

6 If Serum IgG levels are checked, results will be collected

7 The following are Delayed Related AEs of Interest that must be reported to the Sponsor: development of a new malignancy, or neurologic, rheumatologic, autoimmune, or hematologic disorder.

Appendix 2, Table 3 Long-Term Follow-up, Years 6 through 15

Time Point *(years following most recent CAR T cell infusion)*:	6	7	8	9	10	11	12	13	14	15
Procedure Window	±2 months									
Medical history [1,2]	X	X	X	X	X	X	X	X	X	X
PE [1,3]	X	X	X	X	X	X	X	X	X	X
Correlative studies: PB T-cell persistence [4, 5]	X	X	X	X	X	X	X	X	X	X
Serum IgG [6]	X	X	X	X	X	X	X	X	X	X
Delayed Related AEs of Interest [7]	*continuous*									

1 May be performed by local physician or treating oncologist

2 Medical history relevant to subject's disease and treatment, inclusive of infectious disease and use of immunoglobulin replacement, may be obtained by phone unless subject has evidence of ongoing CAR T cell persistence or RCL, in which case subject must be seen in person. If relevant, records pertaining to disease response and/or relapse will be collected.

3 Only required for subjects with evidence of ongoing CAR T cell persistence or RCL.

4 Up to 15mL peripheral blood to CSL.

5 Persistence testing will be discontinued after 2 successive negative results

6 If serum IgG levels are checked, results will be collected.

7 The following are Delayed Related AEs of Interest that must be reported to the study team: development of a new malignancy, or neurologic, rheumatologic, autoimmune, or hematologic disorder

APPENDIX 3: PERFORMANCE STATUS SCALES/SCORE

Performance Status Criteria Karnofsky and Lansky performance scores are intended to be multiples of 10			
Karnofsky subjects ≥ 16 years of age		**Lansky** subjects < 16 years of age	
Score	***Description***	***Score***	***Description***
100	Normal, no complaints, no evidence of disease	100	Fully active, normal
90	Able to carry on normal activity, minor signs or symptoms of disease	90	Minor restrictions in physically strenuous activity
80	Normal activity with effort; some signs or symptoms of disease	80	Active, but tires more quickly
70	Cares for self, unable to carry on normal activity or do active work	70	Both greater restriction of and less time spent in play activity
60	Required occasional assistance, but is able to care for most of his/her needs	60	Up and around, but minimal active play; keeps busy with quieter activities
50	Requires considerable assistance and frequent medical care	50	Gets dressed, but lies around much of the day; no active play, able to participate in all quiet play and activities
40	Disabled, requires special care and assistance	40	Mostly in bed, participates in quiet activities
30	Severely disabled, hospitalization indicated. Death not imminent	30	In bed, needs assistance even for quiet play
20	Very sick, hospitalization indicated. Death not imminent	20	Often sleeping, play entirely limited to very passive activities
10	Moribund, fatal processes progressing rapidly	10	No play, does not get out of bed

APPENDIX 4: GVHD STAGING, GRADING AND DIAGNOSIS INFORMATION

Appendix 4, Table 4 Staging of Acute GVHD

Category	Time of symptoms after HCT or DLI†	Presence of Acute GVHD Features	Presence of Chronic GVHD Features*
Acute GVHD			
Classic acute GVHD	≤ 100 days	Yes	No
Persistent, recurrent or late onset acute GVHD	> 100 days	Yes	No
Chronic GVHD			
Classic chronic GVHD	No time limit	No	Yes
Overlap syndrome	No time limit	Yes	Yes

Appendix 4, Table 5 Grading of Acute GVHD

Severity of Individual Organ Involvement		
Skin	+1	a maculopapular eruption involving less than 25% of the body surface
	+2	a maculopapular eruption involving 25-50% of the body surface
	+3	generalized erythroderma involving >50% of the body surface
	+4	generalized erythroderma with bullous formation and often with desquamation
Liver	+1	bilirubin (2.0-2.9 mg/100ml)
	+2	bilirubin (3-5.9mg/100ml)
	+3	bilirubin (6-14.9mg/100ml)
	+4	bilirubin > 15mg/100ml
Gut	Diarrhea is graded +1 to +4 in severity. Nausea and vomiting and/or anorexia caused by GVHD is assigned as +1 in severity. The severity of gut involvement is assigned to the most severe involvement noted. Subjects with visible bloody diarrhea are at least stage +2 gut and Grade +3 overall	
Diarrhea	+1	≤ 1000 ml of liquid stool/day** (≤ 15ml of stool/kg/day) †
	+2	>1,000 ml of stool/day* (> 15ml of stool/kg/day) †
	+3	>1,500 ml of stool/day* (> 20ml of stool/kg/day) †
	+4	2,000 ml of stool/day* (≥ 25ml of stool/kg/day) †

**In the absence of infectious/medical cause* *continued*
†For pediatric subjects

Appendix 4, Table 2: Grading of Acute GVHD, *continued*

Severity of GVHD	
Grade I	+1 to +2 skin rash
	No gut or liver involvement
Grade II	+1 to +3 skin rash and/or
	+1 gastrointestinal involvement and/or +1 liver involvement
Grade III	+4 skin involvement and/or
	+2 to +4 gastrointestinal involvement and/or
	+2 to +4 liver involvement with or without a rash
Grade IV	Pattern and severity of GVHD similar to Grade 3 with extreme constitutional symptoms or death

From "Graft-vs-host disease" Sullivan, Keith M. *Hematopoietic Cell Transplantation* Ed: D. Thomas, K. Blume, S. Forman, Blackwell Sciences; 1999, pages 518-519

Appendix 4, Table 3 Classification of manifestations for the clinical diagnosis of chronic GVHD

Organ or site	**Diagnostic** *sufficient to establish a chronic GVHD diagnosis*	**Distinctive** *insufficient alone to establish a chronic GVHD diagnosis*	**Common** *seen with both acute and chronic GVHD*
Skin	Poikiloderma Lichen planus-like Sclerotic morphea-like Lichen sclerosis-like	Depigmentation	Erythema Maculopapular Pruritus
Nails		Dystrophy Longitudinal ridging, splitting or brittleness Onycholysis Pterygium ungus Nail loss (usually symmetric and affects most nails)	
Scalp and body hair		New alopecia not due to chemoradiotherapy Scaling, papulosquamous lesions	
Mouth	Lichenoid Hyperkeratotic plaques Diminished oral cavity opening from sclerosis	Xerostomia Mucocele Mucosal atrophy Pseuodmembranes [1] Ulcers [1]	Gingivitis Mucositis Erythema Pain
Eyes		New onset of sicca (dryness, gritty or painful [2]) Cicatricial conjunctivitis Keratoconjunctivitis sicca [2] Confluent areas of punctate keratopathy	
Genitalia	Lichen planus-like Vaginal scarring / stenosis	Erosions [1] Fissures [1] Ulcers [1]	

continued

Appendix 4, Table 3: Classification of manifestations for the clinical diagnosis of chronic GVHD *continued*

Organ or site	**Diagnostic** *sufficient to establish a chronic GVHD diagnosis*	**Distinctive** *insufficient alone to establish a chronic GVHD diagnosis*	**Common** *seen with both acute and chronic GVHD*
GI tract	Esophageal web Esophageal strictures or stenosis in upper to mid third [1]		Anorexia, nausea, vomiting, diarrhea Failure to thrive / weight loss
Liver [3]			Bilirubin > 2x ULN [1] Alk phos > 2x ULN [1] AST or ALT >2x ULN[1]
Lung	Bronchiolitis obliterans [4] (biopsy confirmed)	Bronchiolitis obliterans [4] (based on PFTs and CT scan imaging)	Cryptogenic organizing pneumonia (COP/BOOP)
Muscles, fascia, joints	Fasciitis Joint stiffness or sclerotic contractures	Myositis or polymyositis [2]	

AIHA: autoimmune hemolytic anemia; ALT: alanine aminotransferase; AST: aspartate aminotransferase; BOOP: bronchiolitis obliterans with organizing pneumonia; COP: cryptogenic organizing pneumonia; CT: computerized tomography; ITP: immune thrombocytopenia; PFTs: pulmonary function tests; ULN, upper limit or normal

1 In all cases, infection, drug effects, malignancy, and other cause must be excluded.

2 Diagnosis of cGVHD requires biopsy or radiographic confirmation (or Schirmer test or slit lamp examination for eyes)

3 Because liver histology in acute and chronic GVHD is not distinguishable the diagnosis of cGVHD cannot be made on the basis of biopsy alone and requires a distinctive manifestation in at least one other organ system.

4 Criteria for diagnosing bronchiolitis obliterans: Forced expiratory volume in 1 second/forced (or slow) vital capacity ratio <0.7 and forced expiratory volume in 1 second <75% of predicted and evidence of air trapping or small airway thickening or bronchiectasis

Appendix 4, Table 4 Manifestations acknowledged as chronic GVHD if the diagnosis is already confirmed

Organ or Site	Manifestation
Skin	Sweat impairment, ichthyosis, keratosis pilaris, hypopigmentation, hyperpigmentation
Hair	Thinning scalp hair not otherwise explained (typically patchy, coarse or dull), premature graying
Eyes	Photophobia, periorbital hyperpigmentation, blepharitis (eyelid erythema with edema)
GI tract	Exocrine pancreatic insufficiency
Muscle/Joint	Edema, muscle cramps, arthralgia or arthritis
Hematology	Thrombocytopenia, eosinophilia, lymphopenia
Immune	Hypo-or hyper- gammaglobulinemia, autoantibodies (AIHA, ITP)
Other	Ascites, pericardial or pleural effusions, peripheral neuropathy, nephrotic syndrome, myasthenia gravis, cardiac conduction abnormality, cardiomyopathy

AIHA: autoimmune hemolytic anemia; ITP: immune thrombocytopenia

APPENDIX 5: DEFINITIONS OF CNS AND MARROW STATUS

Definition of CNS status

CNS status is defined as:

- CNS 1: In cerebrospinal fluid (CSF), absence of blasts on cytospin preparation, regardless of the number of white blood cells (WBCs).
- CNS 2: In CSF, presence <5/µL WBCs and cytospin positive for blasts, or >5/µL WBCs but negative by Steinherz/Bleyer algorithm:
  - CNS 2a: <10/µL RBCs; <5/µL WBCs and cytospin positive for blasts;
  - CNS 2b: ≥10/µL RBCs; <5/µL WBCs and cytospin positive for blasts; and
  - CNS 2c: ≥10/µL RBCs; ≥5/µL WBCs and cytospin positive for blasts but negative by Steinherz/Bleyer algorithm (see below).
- CNS 3: In CSF, presence of ≥5/µL WBCs and cytospin positive for blasts (in the absence of a traumatic lumbar puncture) and/or clinical signs of CNS leukemia.

Steinherz/Bleyer algorithm for evaluating traumatic lumbar punctures

If the patient has leukemic cells in the peripheral blood and the lumbar puncture is traumatic and the cytospin contains ≥5 WBC/µL with blasts, the following algorithm should be used to distinguish between CNS 2 and CNS 3 disease:

$$\frac{\text{CSF WBC}}{\text{CSF RBC}} > 2 \times \frac{\text{blood WBC}}{\text{blood RBC}}$$

Therefore, a patient with CSF WBC ≥5/µL blasts, whose CSF WBC/RBC is 2x greater than the blood WBC/RBC ratio, has CNS disease at diagnosis.
For example, the following patient would be classified as CNS3:
CSF WBC = 60/µL; CSF RBC = 1500/µL; blood WBC = 46000/µL; blood RBC = 3.0 X 106/µL:

$$\frac{60}{1500} = 0.04 \quad > 2x \quad \frac{4600}{3.0 \times 10^6} = 0.015$$

Definition of Bone Marrow Status Morphology

- M1 marrow: less than 5% blasts by morphology in bone marrow aspirate
- M2 marrow: 5-25% blasts by morphology in a bone marrow aspirate
- M3 marrow: >25% blasts by morphology in a bone marrow aspirate

APPENDIX 6: DISEASE RESPONSE CRITERIA FOR LEUKEMIA

MRD negative Complete Remission (MRD-CR)
Attainment of M1 marrow with negative MRD (<0.01%) with no evidence of circulating leukemic blasts or extramedullary disease and with recovery of peripheral counts (ANC ≥500/μL and PLT count ≥50,000 μL). Qualifying marrow and peripheral counts should be performed within 1 week of each other.

MRD positive Complete Remission (MRD+CR)
Attainment of M1 marrow with positive MRD (≥0.01%) with no evidence of circulating leukemic blasts or extramedullary disease and with recovery of peripheral counts (ANC ≥500/μL and PLT count ≥50,000 μL). Qualifying marrow and peripheral counts should be performed within 1 week of each other.

MRD-negative Complete Remission without count recovery (MRD-CRi)
Insufficient recovery of platelets (<50,000/ μL) or ANC (<500/μL) but otherwise meets the criteria of MRD-CR.

MRD-positive Complete Remission without count recovery (MRD+CRi)
Insufficient recovery of platelets (<50,000/ μL) or ANC (<500/μL) but otherwise meets the criteria of MRD+CR.

Complete Remission, MRD unknown (CR)
Attainment of M1 marrow with no available MRD results, with no evidence of circulating leukemic blasts or extra medullary disease and with recovery of peripheral counts (ANC ≥500/μL and PLT count ≥50,000 μL). Qualifying marrow and peripheral counts should be performed within 1 week of each other.

Complete Remission without count recovery, MRD unknown (CRi)
Insufficient recovery of platelets (<50,000/ μL) or ANC (<500/μL) but otherwise meets the criteria of CR, MRD unknown.

Partial Remission (PR)
This requires a decrease of at least 50% in the percentage of blasts to a post-treatment value of 5% to 25% in the bone marrow aspirate. (If the pre-treatment blast percentage was 50-100%, this must decrease to a value between 5-25%. If the pre-treatment blast percentage was 20-49%, this must decrease by at least half to a value greater than 5%) with recovery of peripheral counts (ANC >500/μL and platelet count >50,000/μL).

Partial Remission Cytolytic (PRCL)
Complete disappearance of circulating blasts and achievement of at least 50% reduction in bone marrow blast count from baseline.

Minimal Response Cytolytic (MRCL)
≥50% reduction in the peripheral blast count from baseline with no increase in peripheral white blood cell count.

Stable Disease (SD)
This is present when the subject fails to qualify for either MRD-CR, MRD+CR, PR, PRCL, MRCL, or progressive disease (PD).

Progressive Disease (PD)
An increase of at least 25% in the absolute number of circulating leukemic cells from baseline, development of extramedullary disease, or other laboratory or clinical evidence of PD following delivery of chemotherapy.

APPENDIX 7: DISEASE RESPONSE CRITERIA FOR LYMPHOMA

Complete Response (CR)
Imaging reveals complete disappearance of all measurable or evaluable lesions (except bone), no malignant blasts in the bone marrow nor in the CSF

Complete Response unconfirmed (CRu):
Residual mass is negative by FDG-PET, BM and CSF morphologically free of disease

Partial Response (PR)
50% decrease in SPD (sum of product of greatest perpendicular diameters) on imaging (FDG-PET may be positive). Deauville score of 4 or 5 with reduced lesional uptake compared to baseline, no new and /or PD: morphologic evidence of disease may be present in BM or CSF if present at diagnosis, however there should be 50% reduction in the percentage of lymphoma cells

Minor Response (MR)
Greater than 25% but <50% decrease in SPC on imaging; no new and/or PD; morphologic evidence of disease may be present in BM or CSF if present at diagnosis, however there should be 50% reduction in the percentage of lymphoma cells

No Response (NR)
Does not meet CR, PR, MR, or PD

Progressive Disease (PD)
Greater than 25% increase in SPD on imaging, Deauville score of 4 or 5 on FDG-PET with increase in lesional uptake from baseline or development of new morphologic evidence of disease in BM or CSF

APPENDIX 8: ICE AND CAPD SCORING

ICE: Encephalopathy assessement tools for grading of ICANS

Immune effector Cell-associated Encephalopathy (ICE)
• **Orientation:** Orientation to year, month, city, hospital: 4 points • **Naming:** Name 3 objects (e.g., point to clock, pen, button): 3 points • **Following commands:** (e.g., Show me 2 fingers or Close your eyes and stick out your tongue): 1 point • **Writing:** Ability to write a standard sentence (e.g., Our national bird is the bald eagle): 1 point • **Attention:** Count backwards from 100 by ten: 1 point

CAPD: Encephalopathy Assessment for Children <12 years using Cornell Assessment of Pediatric Delirium

Answer the following based on interactions with the child over the course of the shift	**Never 4**	**Rarely 3**	**Sometimes 2**	**Often 1**	**Always 0**
1. Does the child make eye contact with the caregiver?					
2. Are the child's actions purposeful?					
3. Is the child aware of his/her surroundings?					
4. Does the child communicate needs and wants?					
	Never 0	**Rarely** 1	**Sometimes 2**	**Often 3**	**Always 4**
5. Is the child restless?					
6. Is the child inconsolable?					
7. Is the child underactive – very little movement while awake?					
8. Does it take the child a long time to respond to interactions?					

For patients age 1-2 years, the following serve as guidelines to the corresponding questions:

1. Holds gaze. Prefers primary parent. Looks at speaker.
2. Reaches and manipulates objects, tries to change position, if mobile may try to get up
3. Prefers primary parent, upset when separated from preferred caregivers. Comforted by familiar objects (i.e., blanket or stuffed animal)
4. Uses single words or signs
5. No sustained calm state
6. Not soothed by usual comforting actions, for example, singing, holding, talking, and reading
7. Little if any paly, efforts to sit up, pull up, and if mobile crawl or walk around
8. Not following simple directions. If verbal, not engaging in simple dialogue with words or jargon

APPENDIX 9: HIGHLY EFFECTIVE CONTRACEPTION

The following methods of birth control are considered highly effective in preventing pregnancy.

- Total abstinence, when this is in line with the subject's preferred and usual lifestyle. Periodic abstinence like calendar, ovulation, symptothermal, post-ovulation methods, and withdrawal are not acceptable methods of contraception.
- Female sterilization, when the female subject has been surgically sterilized at least 6 weeks prior to enrollment (bilateral oophorectomy or bilateral salpingectomy).
- Male sterilization: the male subject, or female subject's sole sexual partner has been surgically sterilized at least 6 weeks be for enrollment (vasectomy). If the partner of a female subject, appropriate documentation of sterilization should be provided.
- Male subjects: use of a condom during intercourse. In addition, it is advised that the subject's female partner use an additional highly effective method of contraception (hormonal contraception, IUD, etc)
- Use of a combination of any two of the following:
  a. Use of oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate < 1%), for example hormone vaginal ring or transdermal hormone contraception. If oral contraception, subject should be on a stable dose of the same medication for ≥ 3 months prior to enrollment;
  b. Placement of an intrauterine device (IUD) or intrauterine system (IUS);
  c. Use of an occlusive cap (diaphragm or cervical/vault cap) by a female subject, or a condom by a female subject's male partner, combined with a spermicidal foam/gel/film/cream/vaginal suppository.