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CHILDREN'S ONCOLOGY GROUP

ANHL1522

A Pilot Study of Rituximab (RTX) and Third Party Latent Membrane Protein (LMP)-specific Cytotoxic T-Lymphocytes (LMP-TC, [redacted]) in Pediatric Solid Organ Recipients (SOT) with EBV-Positive CD20-Positive Post-Transplant Lymphoproliferative Disease (PTLD)

Phase 2 Study
Limited to U.S. and Canada COG-accredited BMT Programs

CETI at CNMC Supplied Agent:
LMP-specific T cells (LMP-TC, [redacted], NSC# 782666)
IND sponsor for LMP-specific T cells: COG

[redacted]

CONTACT INFORMATION		
To submit site registration documents:	**For patient enrollments:**	**Submit study data**
Regulatory documentation must be submitted to the CTSU via the Regulatory Submission Portal. Regulatory Submission Portal: (Sign in at www.ctsu.org, and select the Regulatory Submission sub-tab under the Regulatory tab.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 to receive further instruction and support. Contact the CTSU Regulatory Help Desk at 1-866-651-2878 for regulatory assistance.	Please refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN) which can be accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org. Contact the CTSU Help Desk with any OPEN-related questions at ctsucontact@westat.com.	Data collection for this study will be done exclusively through Medidata Rave. Please see the Data Submission Schedule in the CRF packet for further instructions.
The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password. Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU RSS.		
For clinical questions (i.e. patient eligibility or treatment-related) contact the Study PI of the Lead Protocol Organization.		
For non-clinical questions (i.e. unrelated to patient eligibility, treatment, or clinical data submission) contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.		
The CTSU Website is located at https://www.ctsu.org.		

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[redacted]

INVESTIGATIONAL SUPPLIED AGENT
LMP-TC NSC# 782666 [redacted]
IND Sponsor: COG

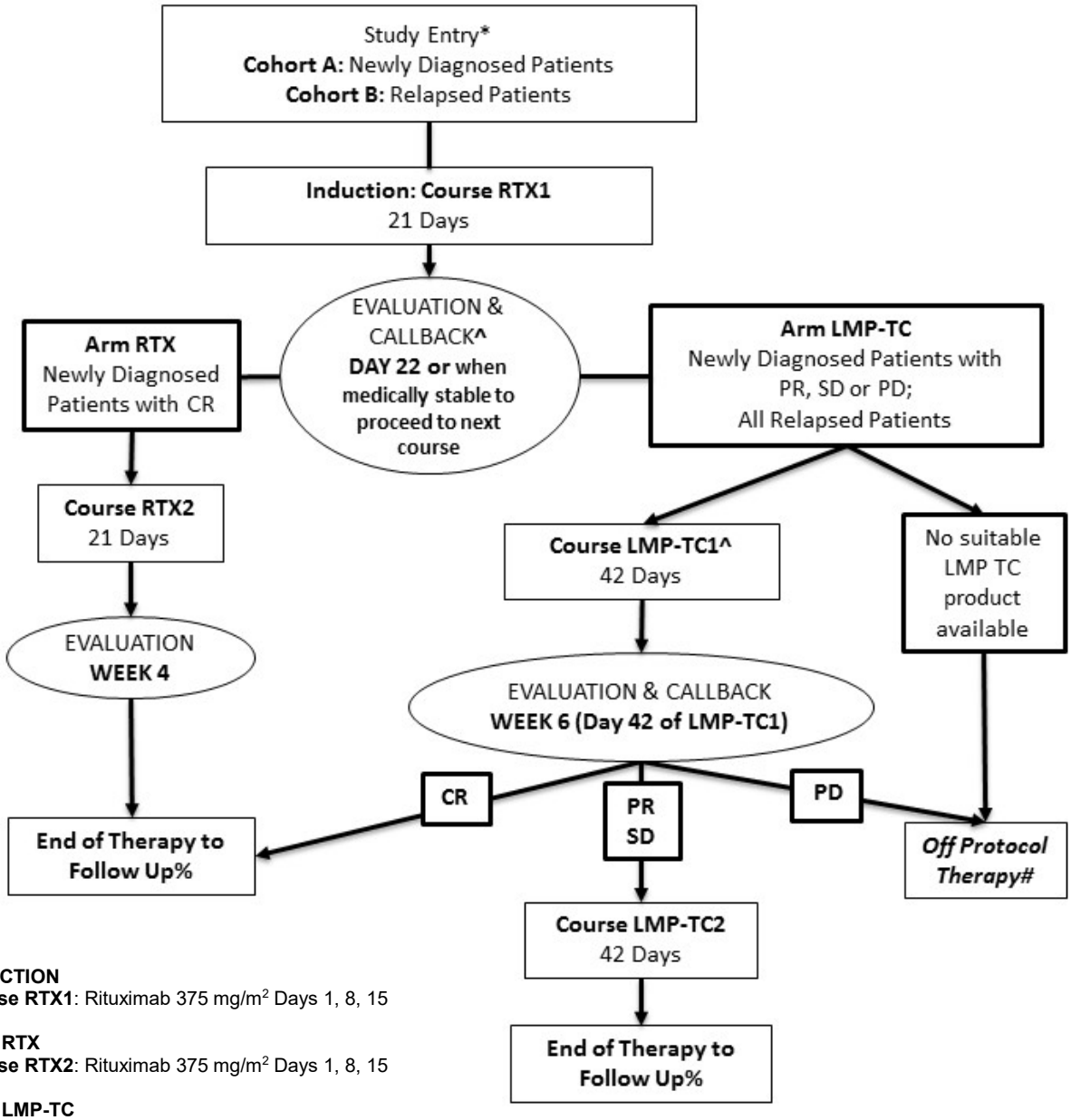
OTHER AGENTS:
Rituximab NSC# 687451 Commercial

SEE SECTION 15 FOR SPECIMEN SHIPPING ADDRESS

ABSTRACT

This is a pilot study of Rituximab (RTX) with or without Third Party Latent Membrane Protein (LMP)-specific Cytotoxic T-Lymphocytes (LMP-specific T cells or LMP-TC) in pediatric and young adult solid organ transplant recipients (SOT) with newly diagnosed, relapsed or refractory EBV-Positive CD20-Positive Post-Transplant Lymphoproliferative Disease (PTLD). EBV-positive PTLD has become the most common form of lymphoproliferation in childhood with an estimated annual incidence of > 100 newly diagnosed patients < 18 years of age in the US. Reduction of immunosuppression with the goal to restore the immunological function of cytotoxic T cells is the first-line therapy with response rates between 20-80% but carries the risk of rejection. Patients who do not respond to reduction of immunosuppression require further therapy and addressing the underlying immunological defect is the next logical step. Preliminary studies have shown that EBV-specific T cells can repair the underlying immunological defect, are well tolerated and have efficacy in PTLD. This pilot study is testing the hypothesis that it is feasible to use Third Party LMP-specific T cells in a cooperative group setting. The production of LMP-specific T cells has become a reproducible procedure with standardized SOPs to generate Good Manufacturing Practice (GMP)-grade LMP-specific T cells. Third Party LMP-specific T cells are readily produced from healthy donors, HLA typed and cryopreserved in cell banks. A Third Party LMP-specific T cells bank, mostly derived from healthy donors, has been established at the Program for Cell Enhancement and Technologies for Immunotherapy (CETI) at Children's National Medical Center and will supply LMP-specific T cells for this study. Untreated newly diagnosed (Cohort A) and relapsed (Cohort B) patients will receive three weekly doses of rituximab followed by a response assessment. Newly diagnosed patients who have a complete response (CR) to rituximab will receive an additional three doses of rituximab because they are predicted to have an excellent outcome. Newly diagnosed patients who do not achieve a CR to 3 doses of rituximab and all relapsed PTLD patients regardless of response will receive LMP-specific T cells. Patients with refractory and/or persistent disease after rituximab according to institutional guidelines are eligible for Cohort C and will proceed straight to LMP-T cell therapy. The closest HLA matched LMP-specific T-cell product will be identified for each patient. At least a 1/6 HLA match with activity through the shared alleles is required. Based on previous experience, it is expected that about 30 different HLA characterized products will cover > 90% of the eligible patients. Participating institutions in this limited institution study will have FACT accredited cell processing and storage facilities and have to adhere to SOPs about dispensing and infusing LMP-specific T cells.

EXPERIMENTAL DESIGN SCHEMA: COHORT A (UNTREATED NEWLY DIAGNOSED PATIENTS) AND COHORT B (RELAPSED PATIENTS)



INDUCTION
Course RTX1: Rituximab 375 mg/m^2 Days 1, 8, 15

ARM RTX
Course RTX2: Rituximab 375 mg/m^2 Days 1, 8, 15

ARM LMP-TC
Courses LMP-TC1 and LMP-TC2: Partially HLA matched Third Party LMP-specific T cells 2 x 10^7/m^2 Days 0 and 7

CR: Complete Response **PR**: Partial Response
SD: Stable Disease **PD**: Progressive Disease

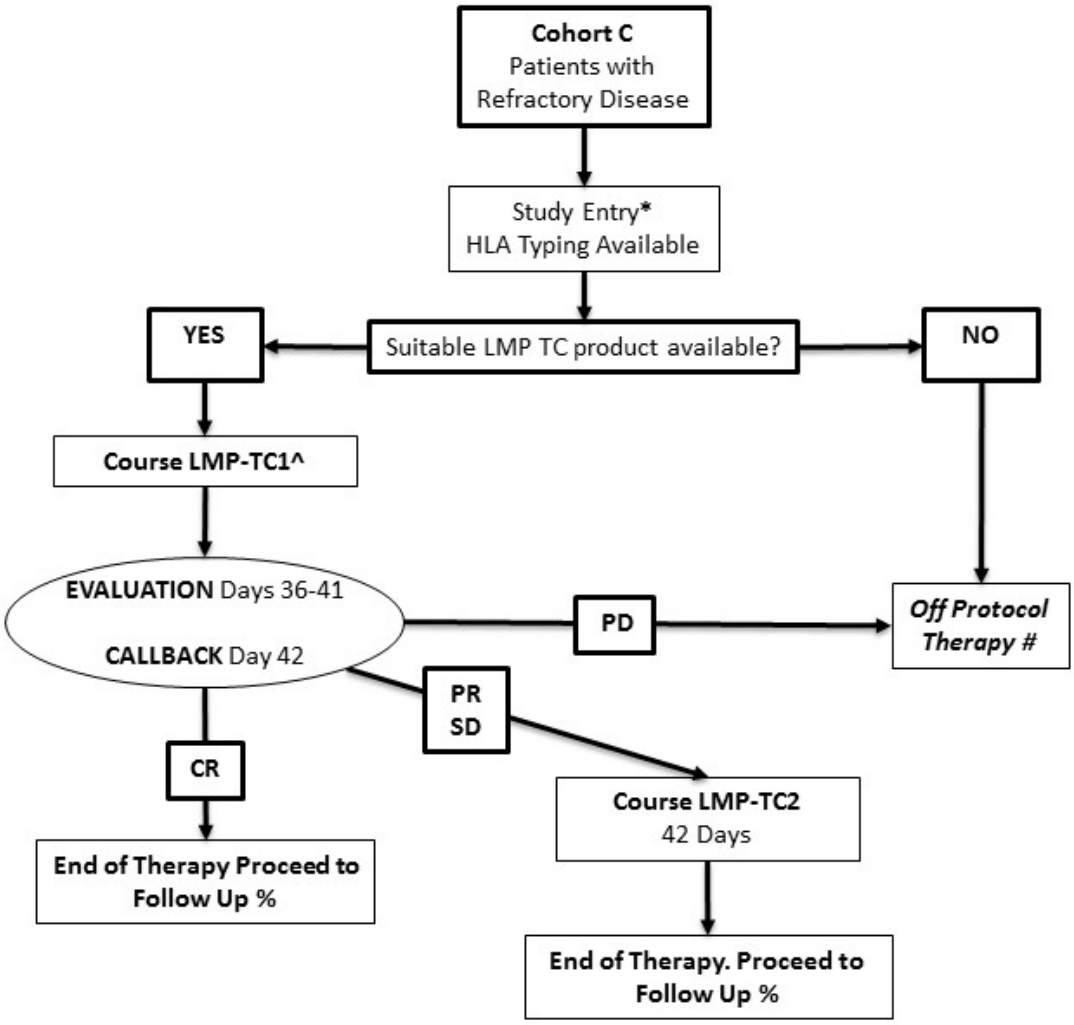
* HLA TYPING results must be submitted by Day 14 of protocol therapy.

^ FIRST LMP-SPECIFIC T CELL ADMINISTRATION (Day 0 LMP-TC1) must be within 2 weeks of Callback date

OFF PROTOCOL THERAPY: chemotherapy is recommended as per institutional guidelines

% END OF PROTOCOL THERAPY: delayed response to RTX and LMP-specific T cells have been described. However, chemotherapy is recommended for patients with PD or SD as per institutional guidelines

EXPERIMENTAL DESIGN SCHEMA: COHORT C (REFRACTORY PATIENTS)



COHORT C

ARM LMP-TC
Courses LMP-TC1 and LMP-TC2: Partially HLA matched Third Party LMP-specific T cells 2 x $10^7/m^2$ given on Days 1 and 8

CR: Complete Response **PR**: Partial Response
SD: Stable Disease **PD**: Progressive Disease

* **HLA TYPING RESULTS MUST BE AVAILABLE AT STUDY ENTRY**

^ First LMP-T CELL ADMINISTRATION (Day 1) must be within 14 days of study enrollment

OFF PROTOCOL TREATMENT: Chemotherapy is strongly recommended as per institutional guidelines

% Delayed response to RTX and/or LMP-specific T cells have been described. However, chemotherapy is strongly recommended for patients with PD or SD as per institutional guidelines

1.0 GOALS AND OBJECTIVES (SCIENTIFIC AIMS)

1.1 Primary Aim

The primary objective of this study is to determine the feasibility of treating pediatric and young adult solid organ transplant recipients who have newly diagnosed, relapsed or refractory EBV-Positive CD20-Positive Post-Transplant Lymphoproliferative Disease (PTLD) with a novel T-cell therapeutic, Third Party Latent Membrane Protein (LMP)-specific T cells, in a cooperative group setting. Feasibility will be based on the percentage of patients assigned to Arm LMP-TC that have a suitable match and receive both T-cell infusions within the prescribed timeframe.

1.2 Secondary Aims

1.2.1 To determine the percentage of eligible patients for whom a suitable LMP-specific T-cell product derived from a Third Party LMP-specific T-cell bank is available.

1.2.2 To estimate the response rate (RR) to three doses of RTX as single agent in children and young adults with newly diagnosed or relapsed EBV-Positive CD20-Positive PTLD after solid organ transplantation (SOT).

1.2.3 To estimate the 2-year event-free survival (EFS) of children and young adults with newly diagnosed, refractory or relapsed EBV-Positive CD20-Positive PTLD after SOT treated with RTX and/or LMP-specific T cells.

1.2.4 To estimate overall survival (OS) of children and young adults with newly diagnosed, refractory or relapsed EBV-Positive CD20-Positive PTLD after SOT treated with RTX and/or LMP-specific T cells.

1.2.5 To estimate the RR to LMP-specific T cells of newly diagnosed (without complete response to Course RTX1), refractory, and relapsed children and young adults with EBV-Positive CD20-Positive PTLD.

1.2.6 To estimate progression-free survival (PFS) of children and young adults with newly diagnosed, refractory or relapsed EBV-Positive CD20-Positive PTLD after SOT treated with RTX and/or LMP-specific T cells.

1.2.7 To describe the toxicity of Third Party LMP-specific T cells in children and young adults with newly diagnosed, refractory or relapsed EBV-Positive CD20-Positive PTLD after SOT treated with RTX and/or LMP-specific T cells.

1.2.8 To validate that absence of EBV viremia correlates with RR, EFS and OS.

1.3 Exploratory Aims

1.3.1 To determine whether Third Party LMP-specific T cells promote autologous immune reconstitution of EBV-specific T cells.

1.3.2 To determine whether EBV viremia is inversely correlated with an increase in EBV-specific T cells *in vivo*.

1.3.3 To determine whether plasma cytokine profile and changes in cytokines over time correlate with treatment response or toxicity (e.g. cytokine release syndrome).

2.0 BACKGROUND

2.1 Introduction

As solid organ transplantation is becoming more common and transplant mortality has decreased, PTLD has quickly become the most prominent form of childhood lymphoproliferative disorder. The estimated incidence of PTLD in pediatric SOT recipients is greater than 100 cases per year in the US.

PTLD has been approached as an infectious problem with EBV as the responsible pathogen, an oncological problem caused by monoclonal proliferation of EBV transformed B cells, and as an immunological problem caused by defective immune surveillance of EBV transformed B cells. The standard first-line approach to PTLD consists of reduction of immunosuppression to restore T-cell function, which repairs the immunological defect.[1] Reduction of immunosuppression leads to resolution in less than 50% of patients and is not always feasible because of increased risk of organ rejection. Thus, > 50% of patients require further therapy beyond reduction of immunosuppression. Other therapeutic approaches have included rituximab as single agent ± chemotherapy or chemotherapy alone with reported EFS rates of only 70% for all approaches.

2.2 Rationale for Development

The outcome for pediatric patients with PTLD after solid organ transplant who do not achieve a complete remission after 3 doses of rituximab are unacceptable with 1-year event-free survival of 53% with rituximab as a single agent reported by the German Ped-PTLD-2005.[2] While the established first-line treatment approach is reduction of immunosuppression to augment an autologous EBV-specific T-cell response,[1] the optimal therapy for patients who do not respond after reduction of immunosuppression remains to be determined.[3] Since the pathogenesis of this tumor is a defective adaptive immune response to EBV, utilizing a therapy to enhance EBV-specific T-cell immunity is a logical treatment approach and the use of EBV-specific T-cell therapies in single centers has been promising.[4,5] Exploring a treatment modality such as LMP-specific T cells, which is not tied to the expression of CD20, may expand the scope of disease controlling therapy beyond other potential therapeutic strategies. Unlike rituximab, chemotherapy, bidirectional T-cell engagers (e.g. blinatumomab) or chimeric antigen receptor T cells, LMP-specific T cells have been shown to: (i) specifically recognize and kill the proliferating EBV-infected B cells and NOT healthy B cells; and (ii) have the potential to repair the underlying immune defect that leads to the development of PTLD, (iii) and do not add to the immune suppression. Repairing this immune defect is critical for achieving a durable treatment response

This protocol tests the hypothesis that targeting the underlying pathologic defect of PTLD with EBV/LMP-specific T cells is feasible in a multi-institution cooperative group setting. In addition, the study will monitor the toxicity of this novel therapy as well as the event-free survival, overall survival, response rate and progression-free survival of pediatric SOT recipients with EBV positive PTLD receiving rituximab with or without LMP-specific T cells.

Cellular therapies including EBV/LMP-specific T cells and chimeric antigen receptor (CAR) T cells are currently in clinical trials and have shown impressive results in B-cell leukemias and lymphomas, but are not yet widely available.[4-6] In PTLD, the proliferating cell population expresses EBV viral proteins found in latency stage III including LMP1

and LMP2 that can be easily targeted using cellular therapy such as EBV-directed T cells (e.g. LMP-specific T cells). In single center pilot studies, administration of Third Party EBV-specific T cells as a single agent therapy led to an overall response rate (CR+PR) of 64% at 5 weeks and 52% at six months without significant toxicities or increased risk of rejection in 33 pediatric and adult SOT recipients, including 13 patients who were refractory to or recurred after prior therapy with rituximab and/or chemotherapy.[5] These results are comparable to the German Ped-PTLD-2005 study, which showed that rituximab as single agent resulted in an EFS of 53%.

ANHL1522 will pilot the use of cellular therapies in the cooperative group setting to assess whether these therapies are feasible in multi-institutional studies. LMP-specific T-cell therapies have the potential to: (i) increase the rate of disease control, (ii) reduce the fraction of patients receiving chemotherapy, (iii) improve the host's adaptive immune response (iv) potentially reduce the dose of rituximab required to achieve a durable CR thereby limiting the use of IVIG and (v) offer a treatment option with potential economic advantages.

If the administration of cellular therapy is proven feasible in a cooperative group setting it will enable future randomized studies evaluating rituximab plus LMP-specific T cells versus "standard of care" (e.g. rituximab alone) with the goal of increasing the patient population treated without chemotherapy from 53% to at least 70%. Additional efforts will include extending the use of LMP-specific T cells to other EBV-associated cancers such as EBV-associated Hodgkin Lymphoma and Diffuse Large B-cell Lymphoma (DLBCL). Further, the success of this study may open the pathway for utilizing Third Party "off-the-shelf" products for other cellular therapy studies in a cooperative group setting. In summary, demonstrating feasibility will greatly expand patients' access to this and other novel cell therapies in the future.

2.3 PTLD after SOT

2.3.1 Incidence

The association of EBV infection, compromised T-cell immunity and B-cell lymphoproliferative disease in patients following transplantation has been known for over 20 years[1]. A cohort study of solid organ transplant recipients from the US Scientific Registry of Transplant Recipients from 1987-2008 including almost 14,000 children showed an overall 2-fold increased risk of cancer compared to the general population but a 7.5-fold excess risk for Non-Hodgkin Lymphoma (NHL).[7] There is a 10-fold increased risk of developing PTLD in the 0-34 years age group compared to the > 50 years age group. In the United States the annual incidence of SOT in pediatric patients rose from 1,397 solid organ transplants in children between the ages of 0-18 in 1990 to 1,825 cases in 2010 based on data from the Organ Procurement and Transplantation Network (OPTN).[8] With the rising incidence of solid organ transplantation in childhood and better long-term survival of the recipients, PTLD has become one of the most common forms of lymphoproliferative disease in childhood. It is estimated based on OPTN data that there are more than 100 newly diagnosed cases each year in the U.S.[8] The incidence ranges from 1-5% in renal transplants to 10-30% in the pediatric lung, small bowel and multiple organ transplants.[1]

2.3.2 Pathology

The most recent WHO classification from 2008 divides PTLD into four groups: mononucleosis-like early lesion (or reactive plasmacytic hyperplasia), polymorphic PTLD, monomorphic PTLD, and Hodgkin-like PTLD.[9] Several single-institution studies and one multi-institution study show an almost equal incidence of mono- and polymorphic PTLD in the pediatric SOT population.[3] More than 90% of pediatric PTLD cases are of B-cell origin, CD20 positive and associated with Epstein Barr virus (EBV) infection. Contrary to bone marrow transplant (BMT) recipients where PTLD is usually of donor origin, PTLD after SOT generally originates in recipient cells.[1]

2.3.3 The Role of EBV in Childhood PTLD

About 80-90% of people will be infected with EBV during their lifetime and the virus persists in latently infected B cells lifelong. An estimated 20-25% of children in developed countries will have acquired EBV by 5 years of age.[10] Since the majority of childhood transplantations occur in the preschool age, the majority of pediatric SOT recipients are EBV naïve at the time of transplant. 60-80% of patients who are EBV naïve at the time of transplant will convert to EBV positivity within three months of transplant either from primary EBV infection or from infection via EBV positive "passenger" donor lymphocytes present in the transplanted organ.[10] In *de novo* infections, EBV enters the body through the oropharyngeal mucosa by transmission through infected saliva.[11] B cells transiting through the oropharynx pick up the virus and disseminate it to the liver, spleen, bone marrow and lymph nodes. The EBV infected B cells progress through several phases of latency that are characterized by differential expression of viral antigens.

In the healthy host, EBV-specific T cells recognize viral antigens expressed by infected B cells and control the infection. EBV persists in a latent stage by down-regulating the expression of viral antigens in infected B cells, thereby rendering the virus invisible to the immune system. Re-expression of viral antigens on the surface of infected dividing B cells leads to periodic expansion of EBV-specific T cells that prevent uncontrolled proliferation of the EBV infected B-cell population to proliferate. In the immunocompromised host, the lack of a robust T-cell immune response permits the uncontrolled proliferation of infected B cells with highest risk of developing PTLD at the time of primary seroconversion.[12] The majority of PTLDs in children derive from EBV infected B cells in latency type III with expression of all viral antigens including the immunogenic EBNA1, 2, 3, LMP 1 and 2 proteins.[4]

Because the prevailing problem in PTLD after SOT consists of the imbalance between EBV infected B cells and EBV-specific T cells, reduction of immunosuppression to restore the immunological function of the cytotoxic T cells is the accepted first line of therapy. This usually leads to resolution in early mononucleosis-like PTLD but is not always feasible because of threat of graft rejection and/or failure and reported success rates in polymorphic and monomorphic PTLD range from only 20-80%.[1] Numerous second-line therapeutic approaches for refractory PTLD in pediatric patients have been explored but generally there has been a paucity of multicenter collaborative studies for this disease. These are generally highly immunogenic tumors that express viral proteins of latency type 3 making them potentially amenable to immune based therapies.

2.4 Previous Studies in PTLD

2.4.1 Cyclophosphamide/Prednisone/Rituximab (CPR) Therapy

The Children's Oncology Group (COG) conducted a phase 2 study of low dose cyclophosphamide (600 mg/m^2, day 1), prednisone (1mg/kg/dose twice daily, days 1-5) and RTX (375 mg/m^2, days 1,8,15 in Cycles 1-2 only) for six cycles in 55 pediatric patients with EBV positive CD20 positive PTLD from 23 centers.[13] 73% of patients had monomorphic disease and 20% had polymorphic disease. Three patients (7.5%) who had more than one site biopsied were found to have both mono- and polymorphic disease in separate locations. Early treatment response rate (CR or PR after the first two cycles of chemotherapy) was 72%. 29 patients achieved a CR by the end of therapy and an additional eight patients of twelve patients with residual disease at the end of therapy achieved a CR post-therapy without any further therapy. The two year event-free survival was 71% and the two-year overall survival was 83%. Ten patients died, seven due to PTLD and three due to infection during therapy.

2.4.2 Rituximab (RTX) in PTLD

Therapy with single agent RTX is the standard of care in PTLD after hematopoietic stem cell transplantation (HSCT) and has rapidly become the most commonly used form of therapy in PTLD after SOT in pediatric patients.[14] RTX as single therapy is widely used in adult solid organ recipients with PTLD with reported CR rate of 60.5%.[15] Preliminary data of a phase 2 study in 40 pediatric SOT recipients with refractory PTLD showed a 69% CR and 16% PR rate for an overall response rate of 85%.[16] Histologies consisted of 17 polymorphic PTLD, 7 monomorphic PTLD, 1 Hodgkin-like, and 1 unspecified histology. A French review reported twenty-six SOT recipients with PTLD between the ages of 3-67 years treated with single agent RTX. There were 10 cases of polymorphic PTLD and 15 cases of monomorphic disease. The overall response rate was 65% (15 CR and 2 PR). Of 15 CRs, 11 patients remained in CR with a median follow-up of 8 months. The United Kingdom Children's Cancer Study Group (UKCCSG) published a retrospective review of rituximab in childhood immunosuppression related lymphoproliferative disease that included 10 SOT recipients and 8 HSCT recipients with PTLD out of 22 patients.[17] The other patients had either primary immunodeficiencies (n=2) or other prolonged acquired immunodeficiency states (n=2). Of the 19 patients with PTLD, 15 patients were treated with single agent rituximab and 5 achieved a CR and 2 a PR for a total response rate of 46.7%. The German Pediatric PTLD phase 2 protocol ("Ped-PTLD2005-Pilot") tested response stratified therapy with patients receiving three weekly doses of RTX at 375 mg/m^2.[18] Patients with CR or PR after three doses of RTX continue with RTX monotherapy while non-responders (NR) are assigned chemotherapy. The one-year EFS using RTX monotherapy for this entire study overall was 53% confirming that much improvement is required for the treatment of this disease beyond using RTX as a single agent therapy. The group of responders (64% of total study population) that was treated with RTX alone had an overall EFS of 81% (Table 1). Long term follow-up data is available on 40 patients. Among the 14 patients who had achieved a CR after three doses of RTX there was only one relapse, confirming that this group of patients has an excellent prognosis. However, in the group of 17 patients who achieved a PR after three doses of rituximab only 11 patients (22.5% of the total study population)

achieved a lasting CR and did not require any chemotherapy. Six patients developed progressive disease and required subsequent chemotherapy (verbal communication by Dr. Maecker-Kohlhoff).

Table 1: Published Data of Chemotherapy and Rituximab in PTLD

Author	Study Size (n)	Therapy	Type of Transplant	Pathology	EBV Status	Outcome
Gross et al., 2002	36	Cyclophosphamide, Prednisone	Liver (17) Liver/small bowel (5) Liver/small bowel/pancreas (1) Small Bowel (3) Kidney (5) Heart (3) Lung (2)	Not reported	positive	CR 75% PR 8% 2-year EFS 69%
Webber et al.	40	Rituximab	Heart (15) Kidney (11) Lung (9) Other (5)	Polymorphic (27) Monomorphic (10) Hodgkin like (2) Nonspecific (1)	38/40 positive	CR 71%, 76% alive at 1.5 year follow-up
Messahel et al.	18	Rituximab	HSCT (8) Liver (5) Heart (4) Kidney (1)	Polymorphic(13) Monomorphic (9)	18/18 positive	CR 8 PR 2
Gross et al.	55	Rituximab, Cyclophosphamide, Prednisone	Heart (11) Liver (17) Kidney (17) Lung (5) Small Bowel (2) Multiple (2)	Polymorphic (8) Monomorphic (29) Mono-and polymorphic (3)	55/55 positive	CR 69% 2-year EFS 71%
Maecker-Kohlhoff et al.	49	Rituximab induction followed by Rituximab only for CR and PR(32) Or Rituximab + mCOMP for SD and PD (17)	Kidney (18) Liver (11) Heart or Lung (20)	Polymorphic (12) Monomorphic B-cell (30) Burkitt (7)	44/49 positive	64% rituximab responders: 81% (53% of total study population) CR with 4.9 year median follow-up; mCOMP: 66% CR rate Estimated 5-EFS of entire study population: 67%

2.5 EBV-specific T-Lymphocytes

The ideal therapy for PTLD would be one that is not toxic and enhances cytotoxicity to B-cell proliferation, but does not increase the risk of allograft rejection and minimizes the inhibition of immune responses required to control EBV driven B-cell proliferation. EBV reactive T cells (EBV-specific T cells) are the primary cellular effector cell population in controlling EBV driven B-cell proliferation but are also targeted by immunosuppression.[12] Suppression of T cells, particularly autologous EBV-specific T cells, is associated with a high risk of developing PTLD. Recent studies in healthy individuals have shown that

primary EBV infection is associated with a CD8+ cytotoxic T-cell response to viral lytic antigens, followed by a CD8+ effector/memory T-cell response against latent viral antigens that persists thereafter and presumably provides lifetime immunosurveillance and protection against EBV B-cell proliferation.[19]

2.5.1 Production of LMP-specific T-Lymphocytes

The production of LMP-specific T cells has become a reproducible and standardized technology.[20]

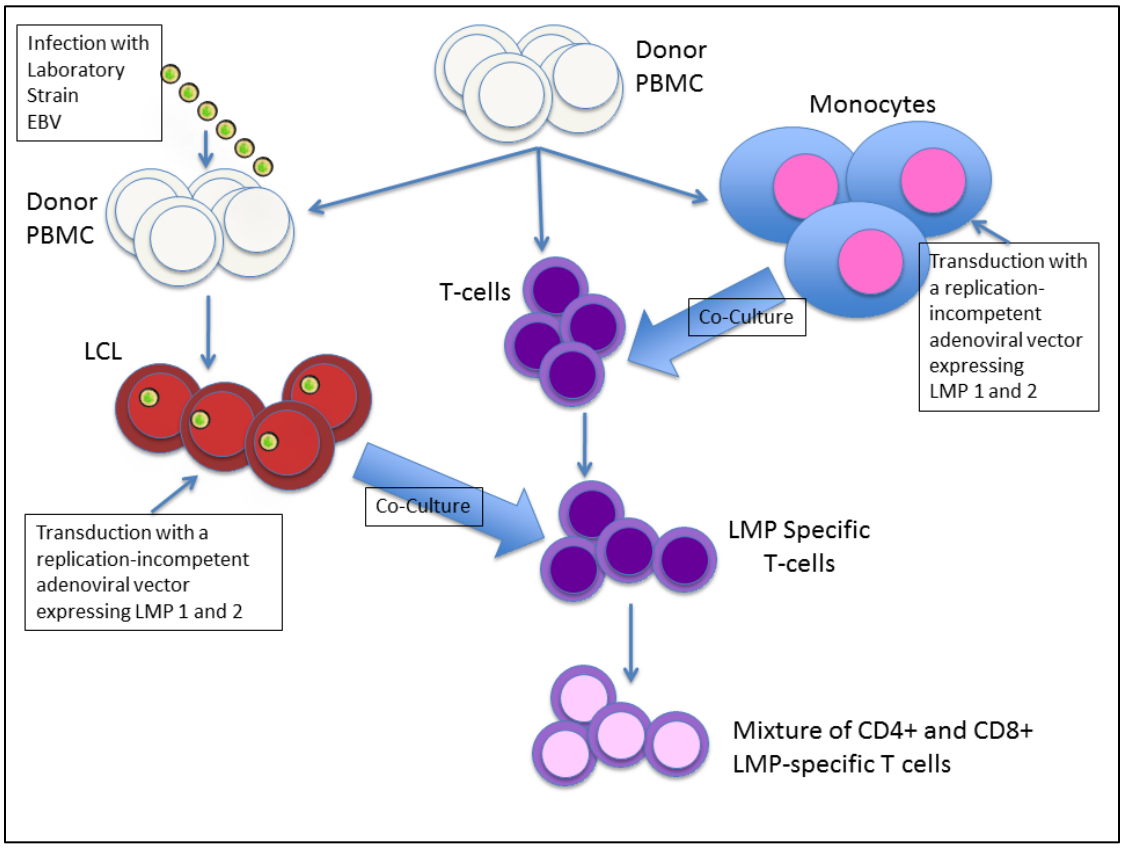


Figure 1: LMP-specific T Cell Production
DC: Dendritic Cells, **EBV**: Epstein-Barr-Virus, **LMP**: Latent Membrane Protein, **PBMC**: peripheral blood mononuclear cells.

In brief, peripheral blood mononuclear cells (PBMCs) are exposed to a laboratory strain of EBV and grown over a period of several weeks into an EBV-infected lymphoblastoid cell line (LCL) that is subsequently transduced with a replication-incompetent adenoviral vector expressing LMP1 and LMP2. In addition, PBMC-derived monocytes are transduced with the same vector to be used as antigen presenting cells (APCs). The genetically modified monocytes are co-cultured with T cells to activate and expand the LMP-specific T cells. The LMP-specific T cells are further expanded through a second stimulation with the genetically modified LCL. The LMP-specific T cells include both CD8- and CD4-positive T cells.[21] The majority of the expanded LMP-specific T cells express an effector memory phenotype (CCR7-/CD62L-), which is important because normal EBV seropositive patients have persistent central and effector memory LMP-specific T

cells subsets, and it is now believed that long-term persistent adoptively transferred virus-specific T cells are derived from central memory T-cell components.[21-23] At the time of cryopreservation of LMP-specific T cells, aliquots undergo extensive quality assurance and control testing including testing for sterility, HLA typing, testing for cytotoxic specificity to avoid allo- and autoreactivity as well as confirmation of absence of genetically modified B cells, monocytes or dendritic cells. This process (including SOPs) has been published by Bollard et al. and has been standardized to manufacture GMP-grade LMP-specific T cells.[20]

2.5.2 Donor-Derived EBV-specific T-Lymphocytes in Allogeneic Hematopoietic Stem Cell transplantation (HSCT)

The most experience using EBV-specific T cells exists in HSCT recipients using donor-derived EBV-specific T cells. T-cell infusions are generally well tolerated by the recipients without any serious side effects, especially without any increase in graft-versus-host disease (GvHD). Used prophylactically, none of the patients developed PTLD. When used therapeutically as single agent, a complete response (CR) was reported in 10/14 patients in the Memorial Sloan Kettering series [6] and 11/13 patients in the Baylor series [24].

2.5.3 EBV-Specific or LMP-Specific T Cells in SOT

Because of the overwhelming use of cadaveric organs, the organ donor does not remain available in the majority of SOTs for the generation of LMP-specific T cells. But even if the donor is available, donor derived LMP-specific T cells are unlikely to be efficacious because PTLD in SOT patients is almost always of recipient origin, and donor and recipient are usually not closely HLA matched. Alternate strategies include the use of autologous EBV-specific T cells and Third Party EBV-specific T cells. Comoli et al. treated three kidney transplant patients with monomorphic PTLD with autologous EBV-specific T cells following polychemotherapy and/or rituximab all of whom achieved complete response and retained allograft function.[25] The use of autologous LMP-specific T cells is limited since the manufacturing is technically challenging. In a study from Baylor College of Medicine, SOT recipients at high risk for PTLD, or with active disease, received autologous T-cell infusions without toxicity. None of the 10 “high risk” patients treated with LMP-specific T cells for high EBV viral loads progressed to PTLD. Two patients received LMP-specific T cells for active disease. One patient with liver PTLD showed a complete response, and one with ocular disease had a partial response stable for over one year.[26] Finally, in another study using LMP-specific T cells, two out of two patients with PTLD went into a durable CR for > 2 years after LMP-specific T-cell therapy without toxicity. One of these patients received LMP-specific T cells as single agent therapy and the other received LMP-specific T cells for persistent disease after chemotherapy and rituximab. A third patient who achieved a CR after rituximab and chemotherapy received LMP-specific T cells and remains in remission for > 2 years.[27]

2.5.4 Third Party EBV-specific T cells

Third Party EBV-specific T cells are readily produced from healthy donors with known HLA phenotypes. The advantages of a cell bank containing HLA-typed EBV-specific T cells are obvious; these cells would be readily available and can be quickly dispensed to matched recipients. Potential downsides may be that less common HLA types may be difficult to match. Third party EBV-specific T cells

have been used in several clinical protocols in SOT recipients with PTLD. They were well tolerated without increased risk of GvHD or graft failure. Response rates vary but are generally favorable. The largest series, a multicenter phase 2 study of 33 SOT and HSCT recipients with PTLD, 13 of whom had failed prior rituximab and/or chemotherapy showed an overall response rate of 64% at 5 weeks and 52% at six months.[5] Better outcomes were observed the closer the EBV-specific T cells were matched to the recipient but generally a match in at least 1-2 antigens is sufficient for activity. In this study, patients received 4 doses of 2×10^6 T cells/kg at weekly intervals. Products were selected for matching by low resolution typing and screened for high level killing of autologous LCLs and low level killing of patient PHA blasts. The degree of HLA matching ranged from 2/6 to 5/6 antigens, and there was a statistically significant trend towards a better outcome at 6 months with better matching. Importantly, no patient developed significant toxicity or GvHD post EBV-specific T cells administration.[5] Based on this data, a suitable match for this study will be defined as at least a 1/6 match as long as the activity is going through the shared allele.

Table 2: Published Data on the Use of EBV-specific T cells in PTLD in SOT recipients

T Cell Source	Study	n	Type of transplant	Side effects	Antiviral Effects
Donor	Baylor/St Jude/Great Ormond Street	113	HSCT	Local inflammation during therapeutic responses	Prophylaxis: no PTLD Treatment: 11/13 CR's
Donor	MSKCC	14	HSCT	None	10 CR 4 PD
Autologous	Comoli et al.	7	SOT	None	Prophylaxis: no PTLD
Autologous	Comoli et al.	5	SOT	None	Therapy: CR
Autologous	Savoldo et al.	12	SOT	None	Prophylaxis: no PTLD Therapy: 1/2 CR
Third party	Haque et al.	33	HSCT and SOT	None	14 CR, 3 PR, 16 NR
Third party	Gandi et al.	3	SOT	None	2/3 CR
Third party	Sun et al.	2	SOT	None	2 CR

Adapted from Bollard et al.[24]

2.5.5 Preliminary Data Using LMP-specific T-cells

The LMP T-cell product that will be used in this study has been developed at Baylor University and Children's National Medical Center.[28] The production process has been previously published.[4]

Patients with EBV-positive non-Hodgkin or Hodgkin lymphoma who either had relapsed after standard therapy or were at high risk for relapse received autologous LMP-TCs at a dose of 2 x 10^7 cells/m^2/week x 2 weeks.[27] Patients with a partial response (PR) or stable disease (SD) were eligible to receive additional doses 8 weeks later. In the patient cohort with relapsed disease, 11 out of 21 patients achieved a CR and an additional 2 patients achieved a PR.[29] One patient suffered CNS deterioration due to disease progression and another patient developed respiratory complications from an intercurrent infection. In both patients, an inflammatory component from LMP-TCs could not be excluded.

Tri-virus specific third party cytotoxic T-lymphocytes (VSTs) with specificity against adenovirus, CMV and EBV were administered at a dose of up to 2 x 10^7 cells/m^2 with additional infusions at an interval of at least 2 weeks in patients who achieved a PR.[29] In 50 recipients, the cumulative rate of CR and PR was 74%. Infusions were well tolerated without any immediate reaction. All patients had been recipients of allogeneic stem cell transplantation. Two developed Grade I de novo GvHD after VSTs. Six patients had a flare of previously diagnosed acute GvHD and one patient had a flare of previously diagnosed chronic GvHD.

2.5.6 Risks of Administering Third Party LMP-specific T cells

Over 65 patients have been treated on the Baylor College of Medicine (BCM) adoptive immunotherapy protocol in which allogeneic donor derived EBV-specific T cells were administered after bone marrow transplantation. The only significant complication was an inflammatory response (cytokine release syndrome) in a patient with bulky EBV lymphoma. In addition, 18 patients have received polyclonal trivirus-specific T cells (i.e. T cells that were selected for EBV, adenoviral, and CMV-reactivity), and 12 patients received adenovirus- and EBV-specific T cells without developing significant adverse events.

None of the patients treated in any of these studies developed significant de novo graft-versus-host disease (GvHD). In other reported studies, none of the patients treated with CMV-specific T cells by Walter et al. developed GvHD.[30] In the cohort of HSCT recipients treated by Peggs et al., 3/13 patients developed mild (grade 1) GvHD; since immunosuppression had been withdrawn early in this study, it is unclear if this side effect was due to T-cell infusion.[31] Although there is theoretically an increased risk of GvHD due to greater mismatch with partially matched T cells, no GvHD was reported in a phase 2 study of closely matched allogeneic T cells in 35 patients or in several case reports using matched T cells.[5,32]

A recent review of the BCM clinical experience with adoptive transfer of allogeneic donor-derived virus-specific T cells in 153 recipients, including 73 instances where there was an HLA mismatch, showed that there was no *de novo* acute GvHD after infusion, and that the incidence of reactivation of pre-existing GvHD was low and not significantly different in recipients of matched or mismatched virus-specific T cells.[4] These data indicate that the adoptive transfer of partially HLA-mismatched virus-specific T cells is safe, even if virus-specific T cells have some cross-reactivity with HLA-mismatched targets in vitro.[33]

In the BCM studies with donor-derived virus-specific T cells, T-cell products were screened for reactivity against other host tissues, such as fibroblasts, PHA blasts

or both, as a release criterion. However, performing such an assay in the current protocol would be difficult for two reasons. First, many recipients may not have pre-treatment lymphocytes available to make PHA blasts. Second, it would add 10 days to the release time, which would adversely affect feasibility and perhaps outcome. Therefore, we will use killing against third party allogeneic PHA blasts rather than patient-derived PHA blasts as a release criterion.

Another potential hazard is the infusion of EBV transformed B cells, which have been co-cultured with the T cells during generation of the T-cell products. This is unlikely to constitute an additional risk to the recipient for several reasons. First, the LCLs are not viable because they have been irradiated with 4,000 cGy and co-cultured with known effectors. In addition, acyclovir is added to the LCL cultures to ensure that no productive virus is present in cultures. Finally, EBV DNA levels will be monitored in peripheral blood by PCR before and after T-cell infusions. The laboratory strain of EBV used for LCL production has not been detected in over 200 patients who have received EBV-specific T cells so far. In addition, the LMP-specific T-cell products are phenotyped prior to infusion and all products have to meet release criteria (< 2% $CD19^+$ B cells in the LMP-specific T-cell product for infusion).

Infusion of cells infected with the adenoviral vector (Ad5f35pp65), could theoretically lead to an inflammatory response due to infectious virus or viral antigens. This is unlikely for several reasons. Firstly, the adenoviral vector is RCA negative. Secondly, in this study we are initially using the adenoviral vector to infect peripheral blood mononuclear cells to stimulate the T cells. We have shown that only CD14-positive cells (monocytes) and not T cells or B cells become infected with the adenoviral vector at the multiplicity of infection (MOI) we use. Subsequent stimulations of the T cells will be with lethally irradiated monocytes and then with EBV-LCL lines transduced with the Ad5f35 vector. Prior to stimulation, the irradiated LCL and monocytes will be washed 4 times which we have shown eliminates 4 logs of free adenovirus from the cultures. Thirdly, adenoviral-specific T cells will be cultured for at least 7 days after the final stimulation with LCL infected with the Ad5f35 vector since pre-clinical studies have shown that this ensures no adenovirus-infected LCL remain alive to be administered to the patients. Finally, we will not infuse any LMP-specific T-cell products that contain > 2% CD19 positive cells (B cells) or > 2% CD14 positive cells (monocytes).

2.6 EBV-specific T cells and Immune Reconstitution

Reduction of immunosuppression leads to resolution of PTLD in some patients by allowing an endogenous immune response to EBV. The German PED-PTLD-2005 showed that chemotherapy suppressed the endogenous EBV T-cell response but rituximab as single agent did not.[18] In addition, Leen et al.[29] showed that Third Party trivirus-specific T cells aided in the immune reconstitution. In that study, deep sequencing of T-cell TCR νβ chains was performed to track T-cell clones over time. Further, in a study of patients who received either donor-derived or Third Party EBV-specific T cells for PTLD after HSCT, a decrease in EBV viremia and an increase in the frequency of EBV-specific T cells was noted in responders.[6] Patients with EBV-associated lymphoma who attained durable clinical responses after receiving autologous LMP-specific T cells demonstrated an increase in the frequency of endogenous T cells specific for non-viral tumor antigens through epitope

spreading.[27] Hence, EBV-specific T cells may have both direct and indirect antitumor activity.

2.7 EBV Viremia, Disease Activity and EBV-specific T cells

It is standard of care to monitor serial EBV PCRs in EBV-naïve patients for at least the first two years post solid organ transplant to detect EBV viremia (as an indication of either primary seroconversion or EBV reactivation) early and be able to intervene with reduction of immunosuppression to prevent PTLD. Reduction in immunosuppression leads to autologous EBV specific immune reconstitution. EBV viremia inversely correlates with the presence of EBV-specific T cells and can predict risk for relapse as shown in previous publications using autologous EBV-specific T cells.[26,27] In addition, Wilsdorf et al. showed in 11 pediatric SOT recipients who had been treated for PTLD that a strong autologous EBV-specific T-cell expansion in response to EBV viremia is capable of preventing relapse and of controlling EBV viremia.[18]. A secondary aim on this study is to further characterize the correlation of EBV viremia, EBV-specific T cells and risk of relapse.

2.7.1 EBV PCR

There is no standardization of quantitative EBV PCR in the US. Each laboratory typically develops an individual cut-off of significant copy numbers, and results are not easily compared between laboratories due to different denominators used. EBV copy numbers have been expressed per plasma volume, amount of total DNA or per lymphocytes making comparison between laboratories virtually impossible. Efforts for standardization are underway, but significant interlab variation is reported according to the WHO international standard.[34]

For that reason, EBV qPCR will be performed centrally at BCM using a cell-based assay which is one of the most sensitive and validated methods.[35]

2.8 Correlative Biology Studies

The goal of the correlative biology studies is to test the hypothesis that LMP-specific T cells aid in the immune reconstitution in patients with EBV positive PTLD. An additional hypothesis is that Third Party LMP-specific T cells may aid in autologous immune reconstitution that persists once the Third Party LMP-specific T cells have been cleared and that EBV viremia as measured by EBV PCR is inversely correlated with absence of EBV-specific T cells.[26,27] If autologous immune reconstitution in response to Third Party LMP-specific T cells occurs it would be expected to reduce the risk of future EBV related lymphoproliferation without the need for persistence of the Third Party LMP-specific T cells or repeated LMP-specific T cells administrations. Both efficacy and toxicity of Third Party LMP-specific T cells will be measured by cytokines directly or indirectly induced through activation of LMP-specific T cells.[36] Variability in specimen quality (e.g. PBMC quantity) is expected so the number of studies performed for each specimen will be adjusted according to feasibility. Correlative biology studies will evaluate:

2.8.1 General Immune Reconstitution and Persistence of LMP-specific T Cells

EBV positive PTLD is caused by a defective immune system. The purpose of these studies is to assess whether Third Party LMP-specific T cells are aiding in the immune reconstitution of the recipients by functioning as a bridge to autologous EBV specific immune reconstitution. Monitoring occurrence and persistence of this immune reconstitution may be able to predict response and/or risk of recurrence of PTLD. To explore this possibility, T-cell immunophenotyping,

cytokine receptor expression and measurement of cytokine releases will be performed. These results will be correlated with serial EBV qPCR.

2.8.2 Persistence of LMP-specific T cells and Immunity to EBV

EBV lymphoproliferation is controlled by the presence of EBV-specific T cells. Persistent absence of EBV viremia as measured by EBV PCR in the blood is able to predict the presence of EBV-specific T cells which reduces the risk of recurrence. The rationale behind this correlative study is that it is currently unknown what the adequate post-therapy monitoring is for this patient population that receives ongoing immune suppression. Serial CT and/or PET scans carry significant radiation exposure. Developing reliable biomarkers would be of significant clinical importance to avoid unnecessary radiation exposure and/or invasive procedures. For this purpose, HLA-tetramer assays to assess T-cell frequencies and EBV PCRs will be performed serially.

2.8.3 Dynamic Production of Inflammatory Cytokines as a Measure of Efficacy and Toxicity.

Plasma inflammatory proteins reflect the cumulative elaboration of cytokines and chemokines produced by effector T cells as well as by host immune responses. We hypothesize that specific patterns of cytokine/chemokine expression will predict response to therapy as well as toxicity in patients with PTLD treated with Third Party LPM-specific T cells.

2.9 **Future Development of Third Party LMP-specific T cells**

Third Party LMP-specific T cells can be produced from healthy donors, and can be stored and made readily available without delay when needed. If found that they also aid in autologous immune reconstitution without the need of persistence, further clinical development of third party cellular therapy would be indicated because they could be widely and easily available without the need and delays of “custom-made” cellular therapies and without the unknown risks of persistence of modified cells in the host. Future plans include extending their use in the cooperative group setting to other EBV positive malignancies such as Hodgkin Disease. In addition, if the use of Third Party “off the shelf” cellular products is shown to be efficacious this may be studied in other cellular products as such chimeric antigen receptor T cells and lead to a much wider availability of those products as well.

3.0 STUDY ENROLLMENT PROCEDURES AND PATIENT ELIGIBILITY

Prior to patient enrollment on ANHL1522, sites must ensure FACT accreditation and COG approval as a transplant center. (See COG member website Administration page under the Membership tab for the link to the list of Approved COG Transplant Centers.)

3.1 Study Enrollment

3.1.1 Patient Registration

Prior to enrollment on this study, patients must be assigned a COG patient ID number. This number is obtained via the Patient Registry module in OPEN following authorization for the release of protected health information (PHI). The COG patient ID number is used to identify the patient in all future interactions with COG. If you have problems with the registration, please refer to the online help. For additional help or information, please contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

A Biopathology Center (BPC) number will be assigned as part of the registration process. Each patient will be assigned only one BPC number per COG Patient ID. For additional information about the labeling of specimens please refer to the Pathology and/or Biology Guidelines in this protocol.

Please see Appendix I for detailed CTEP Registration Procedures for Investigators and Associates, and Cancer Trials Support Unit (CTSU) Registration Procedures including: how to download site registration documents; requirements for site registration, submission of regulatory documents and how to check your site's registration status.

NOTE: In order for an institution to maintain COG membership requirements, every patient with a known or suspected neoplasm needs to be offered participation in APEC14B1, *Project:EveryChild A Registry, Eligibility Screening, Biology and Outcome Study*.

3.1.2 IRB Approval

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll patients. Assignment of site registration status in the CTSU Regulatory Support System (RSS) uses extensive data to make a determination of whether a site has fulfilled all regulatory criteria including but not limited to the following:

- An active Federal Wide Assurance (FWA) number
- An active roster affiliation with the Lead Network or a participating organization
- A valid IRB approval
- Compliance with all protocol specific requirements.

In addition, the site-protocol Principal Investigator (PI) must meet the following criteria:

- Active registration status
- The IRB number of the site IRB of record listed on their Form FDA 1572
- An active status on a participating roster at the registering site.

For information about the submission of IRB/REB approval documents and other regulatory documents as well as checking the status of study center registration packets, please see Appendix I.

Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support.

Note: Sites participating on the NCI CIRB initiative and accepting CIRB approval for the study are not required to submit separate IRB approval documentation to the CTSU Regulatory Office for initial, continuing or amendment review. For sites using the CIRB, IRB approval information is received from the CIRB and applied to the RSS in an automated process. Signatory Institutions must submit a Study Specific Worksheet for Local Context (SSW) to the CIRB via IRBManager to indicate their intent to open the study locally. The CIRB's approval of the SSW is then communicated to the CTSU Regulatory Office. In order for the SSW approval to be processed, the Signatory Institution must inform the CTSU which CIRB-approved institutions aligned with the Signatory Institution are participating in the study. Other site registration requirements (e.g., laboratory certifications, protocol-specific training certifications, or modality credentialing) must be submitted to the CTSU Regulatory Office or compliance communicated per protocol instructions.

3.1.3 Reservation Requirements

Prior to obtaining informed consent and enrolling a patient, a reservation must be made following the steps below. Reservations may be obtained 24 hours a day through the Oncology Patient Enrollment Network (OPEN) system.

Cohort A: Newly Diagnosed
Cohort B: Relapsed
Cohort C: Refractory

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

If the study is active, a reservation can be made by following the steps below:

1) Log in to https://open.ctsu.org/open/ using your CTEP IAM user name and password.
2) In order to make a reservation, the patient must have an OPEN patient number. Click on the 'Slot Reservation' tab to create an OPEN patient number, under 'Patients'.
3) Using the OPEN patient number '**RESERVE'** a slot for that patient.

4) On the 'Create Slot Reservation' page, select the Protocol Number, enter the COG Patient ID, and choose the required stratum (if applicable) in order to obtain a reservation.

   Refer to the 'SITE – Slot Reservation Quick Reference' guide posted under the 'Help' tab in OPEN for detailed instructions: https://www.ctsu.org/readfile.aspx?fname=OPEN/OPEN_SlotReservation_QuickReference_SiteUserGuide_102612.pdf&ftype=PDF

3.1.4 Study Enrollment

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available on a 24/7 basis. To access OPEN, the site user must have an active CTEP-IAM account (check at https://ctepcore.nci.nih.gov/iam) and a 'Registrar' role on either the lead protocol organization (LPO) or participating organization roster.

All site staff will use OPEN to enroll patients to this study. It is integrated with the CTSU Enterprise System for regulatory and roster data and, upon enrollment, initializes the patient position in the Rave database. OPEN can be accessed at https://open.ctsu.org or from the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org. To assign an IVR or NPIVR as the treating, crediting, consenting, drug shipment (IVR only), or investigator receiving a transfer in OPEN, the IVR or NPIVR must list on their Form FDA 1572 in RCR the IRB number used on the site's IRB approval. If a DTL is required for the study, the IVR or NPIVR must also be assigned the appropriate OPEN-related tasks on the DTL.

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

- All eligibility criteria have been met within the protocol stated timeframes.
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

Further instructional information is provided on the CTSU members' web site OPEN tab or within the OPEN URL (https://open.ctsu.org). For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

3.1.5 Timing

Patients must be enrolled before treatment begins. The projected start date of protocol therapy for Cohorts A and B must be no later than **five (5)** calendar days after the date of study enrollment. For patients in Cohort C, the first dose of LMP-TC must be administered within 14 days of study enrollment. **Patients who are started on protocol therapy prior to study enrollment will be considered ineligible**.

All clinical and laboratory studies to determine eligibility must be performed within 7 days prior to enrollment unless otherwise indicated in the eligibility section below.

Cohorts A and B: HLA typing must be sent at study enrollment and results must be available *by Day 14* for identification of available matched LMP-specific T cell product in time for treatment assignment.

Cohort C: HLA typing must be AVAILABLE at study enrollment for identification of available matched LMP-specific T cell product in time for treatment to be administered within two weeks from study enrollment. Patients without HLA typing available at the time of enrollment are ineligible.

3.1.6 **Cohorts A and B: Callback by Day 22 for Post Induction Treatment Assignment**
Response evaluation followed by a Callback, which is performed in OPEN as a Step 2 Registration, should be submitted by Day 22 or as soon as a patient is medically stable to proceed to the next cycle. Reasons for delays in submitting Callback should be documented in the medical chart. Assignment to Arm RTX or Arm LMP-TC (LMP-specific T cells) will be based on the patient's response to Induction.

If HLA typing is not available by the Callback: patients assigned to Arm LMP-TC will immediately be taken off protocol therapy (patients assigned to Arm RTX proceed with protocol therapy).

Timing is Critical: For patients assigned to Arm LMP-TC who have a suitably matched LMP-specific T-cell product, Course LMP-TC1 therapy must begin within 2 weeks of the date of the Callback.

3.1.7 Post Course LMP-TC1 Evaluation and Treatment Assignment
For patients on Arm LMP-TC, a response evaluation and Callback must be submitted by Day 42 of Course LMP-TC1. Patients with PR or SD after LMP-TC1 and available suitably matched LMP-specific T-cell product will proceed to Course LMP-TC2. Patients with CR or PD after LMP-TC1 will go off protocol therapy.

3.2 Patient Eligibility Criteria

Important note: The eligibility criteria listed below are interpreted literally and cannot be waived. All clinical and laboratory data required for determining eligibility of a patient enrolled on this trial must be available in the patient's medical/research record which will serve as the source document for verification at the time of audit.

All clinical and laboratory studies to determine eligibility must be performed within 7 days prior to enrollment unless otherwise indicated. Laboratory values used to assess eligibility must be no older than seven (7) days at the start of therapy. Laboratory tests need not be repeated if therapy starts within seven (7) days of obtaining labs to assess eligibility. If a post-enrollment lab value is outside the limits of eligibility, or laboratory values are > 7 days old, then the following laboratory evaluations must be re-checked within 48 hours prior to initiating therapy: CBC with

differential, bilirubin, ALT (SGPT) and serum creatinine. If the recheck is outside the limits of eligibility, the patient may not receive protocol therapy and will be considered off protocol therapy. Radiographic imaging, endoscopic exams with biopsies, lumbar punctures, and bone marrow exams do not need to be repeated if done within 14 days prior to study entry.

Immunosuppression: Patients and their treating physician must agree to maintain adequate immunosuppression during LMP TC cycles following guidelines to at least maintain minimal levels of either a calcineurin and/or a MTOR inhibitor as outlined in Section 4.4.5.

For Cohort A & B: See Section 4.2.2 for required studies to be obtained at baseline prior to starting protocol therapy.
For Cohort C: See Section 4.4.2 for required studies to be obtained at baseline prior to starting protocol therapy.

3.2.1 Age
Patients must be < 30 years of age at the time of enrollment.

3.2.2 Diagnosis

3.2.2.1 Patient must have a history of solid organ transplantation.

3.2.2.2 Patients must have biopsy-proven newly diagnosed, relapsed or refractory polymorphic or monomorphic PTLD using the WHO classification and that is:

3.2.2.2.1 CD20 positive

3.2.2.2.2 EBV positive by EBER in situ hybridization (preferred) and/or LMP immunoperoxidase staining.

3.2.2.3 There must be evaluable disease at study entry either by imaging or by serial endoscopic biopsies.
Note: as indicated in Section 10.2.5.1 a measurable node must have an LDi (longest diameter) greater than 1.5 cm. A measurable extranodal lesion should have an LDi greater than 1.0 cm. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

3.2.2.4 Patients must be considered medically refractory to decreased immunosuppression (50% or greater reduction) for at least 1 week or there must be documentation in the medical chart that decreased immunosuppression would be associated with an unacceptable risk of rejection.

3.2.3 Performance Level
Patients must have a performance status corresponding to ECOG scores of 0 or 1. Use Karnofsky for patients > 16 years of age and Lansky for patients ≤ 16 years of age. See

https://cogmembers.org/site/pages/default.aspx?page=Prot_reference_materials under Standard Sections for Protocols.

3.2.4 Life Expectancy

Patients must have a life expectancy of ≥ 8 weeks.

3.2.5 Prior Therapy

Patients must have fully recovered from the acute toxic effects of all prior chemotherapy, immunotherapy, or radiotherapy prior to entering this study.

a. Myelosuppressive chemotherapy: Must not have received within 2 weeks of entry onto this study.

b. Biologic (anti-neoplastic agent):

- Cohort A and B: Patient must not have received therapy with anti-CD20 monoclonal antibodies within 90 days of entry onto this study.
- Cohort C: Patient must have received Rituximab at 375 mg/m^2 weekly for at least 3 doses within the last 90 days prior to study enrollment.

c. Radiation therapy (RT): Must not have received any prior radiation to any sites of measurable disease.

d. Stem Cell Transplant (SCT): Must not have received any prior stem cell transplant.

e. Investigational Therapy: Must not have received investigational therapy within 30 days of entry onto this study.

f. Cellular Therapy: Must not have received prior EBV or LMP-specific T cells within 90 days of entry onto this study.

g. T-cell Antibodies: Must not have received alemtuzumab or other anti-T-cell antibody therapy within 28 days of entry onto this study.

Please see Section 4.1.3 for the concomitant therapy restrictions for patients during treatment.

3.2.6 Cohort C Only: HLA typing is available and will be submitted at the time of enrollment.

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3.2.7 Exclusion Criteria

3.2.7.1 Burkitt morphology.

3.2.7.2 CNS involvement.
CNS status must be confirmed by lumbar puncture.
Note: Lumbar puncture can be performed at the time of diagnosis and does not need to be repeated unless there is a change in neurological status or it was performed more than 14 days prior to study entry.

3.2.7.3 Bone marrow involvement (>25%).

Note: Bone marrow aspiration/biopsy can be performed at the time of diagnosis and does not need to be repeated unless there is a change in peripheral blood counts or it was performed more than 14 days prior to study entry.

3.2.7.4 Fulminant PTLD defined as:
Fever > 38°C, hypotension, and evidence of multi-organ involvement/failure including two or more of the following:
1) Bone marrow (including pancytopenia without any detectable B-cell proliferation)
2) Liver (coagulopathy, transaminitis and/or hyperbilirubinemia)
3) Lungs (interstitial pneumonitis with or without pleural effusions)
4) Gastrointestinal hemorrhage

3.2.7.5 Any documented donor-derived PTLD.

3.2.7.6 Infections:

3.2.7.6.1 Hepatitis B or C serologies consistent with past or current infections because of the risk of reactivation with rituximab.

3.2.7.6.2 Severe and/or symptomatic refractory concurrent infection other than EBV.

3.2.7.7 Pregnancy and Breast Feeding.

3.2.7.7.1 Pregnant females are ineligible since there is no available information regarding human fetal or teratogenic toxicities.

3.2.7.7.2 Lactating females are not eligible unless they have agreed not to breastfeed their infants.

3.2.7.7.3 Female patients of childbearing potential are not eligible unless a negative pregnancy test result has been obtained.

3.2.7.7.4 Sexually active patients of reproductive potential are not eligible unless they have agreed to use an effective contraceptive method for the duration of their study participation and for 12 months following completion of study therapy.

3.2.8 Regulatory Requirements

3.2.8.1 All patients and/or their parents or legal guardians must sign a written informed consent.

3.2.8.2 All institutional, FDA, and NCI requirements for human studies must be met.

4.0 TREATMENT PROGRAM

Timing of protocol therapy administration, response assessment studies, and surgical interventions are based on schedules derived from the experimental design or on established standards of care. Minor unavoidable departures (up to 72 hours) from protocol directed therapy and/or disease evaluations (and up to 1 week for surgery) for valid clinical, patient and family logistical, or facility, procedure and/or anesthesia scheduling issues are acceptable (except where explicitly prohibited within the protocol).

4.1 Overview of Treatment Plan

4.1.1 Cohorts A & B Induction: Rituximab

All patients will receive a 21-day course of rituximab or biosimilar at 375 mg/m^2/dose on Days 1, 8, 15. **Results of HLA typing must be available by the end of Week 2 (Day 14) of Induction for determination of availability of a suitable LMP-specific T-cell product.**

The HLA typing must be performed at an ASHI accredited laboratory and needs to include at a minimum low resolution typing at A, B and DR. Previous typing (e.g. HLA typing done for transplant evaluation) is acceptable.

See Section 16.0 for imaging guidelines. A response evaluation during Week 3 (Days 18-21) of Induction will be followed by a Callback (see Section 3.1.6), which must be completed by Day 22 or as soon as a patient is medically stable to proceed to the next cycle. Reasons for delays in submitting Callback should be documented in the medical chart.

If HLA typing is not available by the Callback: patients assigned to Arm LMP-TC will immediately be taken off protocol therapy (patients assigned to Arm RTX continue on therapy).

4.1.2 Assignment to Arm RTX or Arm LMP-TC

Based on response to Induction therapy, patients will be assigned to either Arm RTX or Arm LMP-TC as outlined below.

4.1.2.1 Arm RTX

Cohort A: Newly diagnosed patients who achieve a complete response (CR) after Induction will be assigned to Arm RTX to receive a second 21-day course of rituximab or biosimilar (Course RTX2).

4.1.2.2 Arm LMP-TC

Cohort A: Newly diagnosed patients who do not achieve a complete response (CR) after Induction will be assigned to Arm LMP-TC.

Cohort B: All relapsed patients will be assigned to Arm LMP-TC after induction regardless of response.

Cohort C: All patients with refractory disease who have received rituximab (or biosimilar) within 90 days according to institutional guidelines are assigned to Cohort C and proceed directly to Arm LMP-

TC at enrollment.

Patients assigned to Arm LMP-TC without a suitable LMP-specific T-cell product will go off protocol therapy. Further treatment with chemotherapy is at the discretion of the treating physician.

IMMUNOSUPPRESSION

Patients assigned to Arm LMP-TC are required to have minimum levels of either calcineurin inhibitors and/or MTOR inhibitors at the start of the course and must maintain these minimum levels throughout the course, as follows:

Calcineurin Inhibitors

Tacrolimus (dose range per institutional guidelines) to achieve minimum level of 4 ng/ml

or

Cyclosporine (dose range per institutional guidelines) to achieve minimum level of 100 ng/ml

and/or

MTOR Inhibitors

Sirolimus (dose range per institutional guidelines) to achieve minimum level of 4 ng/ml

or

Everolimus (dose range per institutional guidelines) to achieve minimum level of 3 ng/ml

For patients on combination therapy, the minimum level needs to be maintained at least for the calcineurin inhibitors.

Close monitoring of immunosuppression as per institutional guidelines is required. Calcineurin inhibitor and/or MTOR inhibitor levels are required weekly. If levels are subtherapeutic, adjust dose(s) as per institutional guidelines and repeat levels approximately every 48-72 hours until the therapeutic range has been reached. See Section 4.4.5

Course LMP-TC1 (42 days): Patients with a suitable LMP-specific T-cell product will receive the closest HLA matched product at a dose of 2 x 10^7cells/m^2/dose on Days 0 and 7 followed by a response evaluation completed during Days 36-41 and submitted via the Callback form by Day 42 (see Section 3.1.7). Patients with CR at the end of LMP-TC1 have completed protocol therapy. Patients with PD at the end of LMP-TC1 go off protocol therapy with a recommendation to receive further chemotherapy per institutional guidelines.

Course LMP-TC2 (42 days): Patients with PR or SD after LMP-TC1 and with a suitable product available will be assigned to Course LMP-TC2 to receive two additional doses of LMP-specific T cells.

1. If the patient had a PR and a sufficient number of vials of cells remain, the LMP-TC2 doses should come from the same product used in LMP-TC1.
2. If the patient had SD and/or insufficient cells remain in the original product, the LMP-TC2 doses may be selected from another product if an additional suitably matched product is available.

Except for the Induction course (RTX1) up to the start of Arm LMP-TC or Arm RTX, all patients with progressive disease during protocol therapy will be taken off protocol therapy to receive chemotherapy according to institutional guidelines.

4.1.3 Concomitant Medications

4.1.3.1 Concurrent immunosuppression (e.g., calcineurin inhibitors, mycophenolate mofetil, sirolimus, azathioprine, etc.) to prevent organ rejection is allowed.

4.1.3.2 Corticosteroids are not allowed in excess of 0.5 mg/kg/day in prednisone equivalents within 7 days of LMP-specific T-cell administration or during Courses LMP-TC1 or LMP-TC2 because the activity of LMP-specific T cells are inhibited by high dose corticosteroids. The only exception is for emergency treatment of allergic/anaphylactic reactions as outlined in Appendix III.

4.1.3.3 Alemtuzumab or other anti-T-cell antibody therapies are not allowed during protocol therapy.

4.1.3.4 Investigational drugs or therapies are not allowed during protocol therapy.

4.1.4 Supportive Care

4.1.4.1 Anaphylaxis:
Because of the risk of allergic and/or anaphylactic reaction, rituximab and LMP-specific T-cell infusions should be given in a monitored setting with resuscitation equipment, diphenhydramine, epinephrine and corticosteroids (hydrocortisone or methylprednisolone) readily available.

4.1.4.2 Management of other adverse events possibly, probably or definitely related to LMP-specific T cells:
Please refer to Appendix III for detailed management instructions of early and late reactions to LMP specific T cells.

4.1.4.3 Immunoglobulins:
Patients who develop hypogammaglobulinemia (defined as IgG levels below the institutional lower limit of normal for age) should receive IVIG replacement every 3-4 weeks until normal values are maintained.

For COG Supportive Care Guidelines see:
https://childrensoncologygroup.org/index.php/cog-supportive-care-guidelines .

4.2 COHORT A & B: Induction-Rituximab (RTX1) for Untreated Newly Diagnosed or Relapsed Patients

4.2.1 Therapy Delivery Map – Induction: RTX1 Rituximab (RTX) Induction lasts 21 days and begins on Day 1.	_____ Patient COG ID number _____ DOB

This TDM is on 2 pages.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
Rituximab or biosimilar (RTX)	IV	375 mg/m^2/dose	1, 8, 15	Please refer to Appendix II for detailed rituximab (or biosimilar) administration guidelines, including recommended premedication and monitoring during infusion.

Ht _____cm Wt _____kg BSA _____m^2

Date Due	Date Given	Day	RTX or biosimilar _____mg	Studies
			Enter calculated dose above and actual dose administered below	
		1	_____mg	a-d, f-m
		8	_____mg	f-k
		15	_____mg	f-k
		18		l
		21		e-k, m

Complete Callback (Section 3.1.6) by Day 22 (or as soon as a patient is medically stable to proceed to the next cycle) for treatment assignment to Arm RTX (Section 4.3) or Arm LMP-TC (Section 4.4).

See Section 5.0 for Dose Modifications including management of infusion-related reactions, and see Section 4.1.4 for Supportive Care Guidelines.

4.2.2 Required Observations in Induction

All baseline studies must be performed prior to starting protocol therapy. Unless otherwise indicated, observations a-m can be performed up to 7 days prior to the start of therapy. Radiographic imaging and/or endoscopy with biopsies, bone marrows, or lumbar punctures do not need to be repeated as long as they were obtained within 14 days prior to enrollment.

a. HLA Typing from ASHI-accredited laboratory. Results required by Day 14. Must be at minimum low resolution typing at A, B and DR. Previous typing done for transplant evaluation is acceptable.

b. Height/ BSA.

c. Hepatitis B and C serologies.

d. Pregnancy Test: Female patients of childbearing potential require a negative pregnancy test prior to starting Induction.

e. Repeat bone marrow aspiration and biopsy on Day 21 is required only for patients with a positive BM at diagnosis.

f. History and Physical Exam, Vital Signs, Performance Status, Weight.

g. CBC, diff.

h. Electrolytes, BUN, creatinine: for all patients at Baseline and Day 21. Note: interim weekly evaluations are required only for patients with renal transplant.

i. AST, ALT, total and direct bilirubin, albumin, total protein, LDH: for all patients at Baseline and Day 21. Note: interim weekly evaluations are required only for patients with liver transplant.

j. Documentation of immunosuppressive medication.

k. If applicable: tacrolimus, sirolimus, cyclosporine level. If levels are subtherapeutic, adjust dose(s) as per institutional guidelines and repeat levels approximately every 48-72 hours until the therapeutic range has been reached.

l. CT with contrast of involved areas: Baseline scan and response evaluation between Days 18-21. See Section 10.2 specifics for use of MRI or PET in addition to or as an alternative modality to CT. Patients with GI tract involvement require endoscopy with biopsies if they do not have measurable disease by imaging.

m. EBV PCR: 5 mL whole Blood in EDTA (purple top). Submission to BCM for centralized assay. See Section 15 for specimen collection and shipment instructions.

This listing only includes evaluations necessary to answer the primary and secondary aims. OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD CLINICAL CARE.

Comments
(Include any held doses, or dose modifications)

4.2.3 Induction (RTX1): Newly Diagnosed and Relapsed Patients

See Appendix II for rituximab infusion guidelines and Section 4.1.4 for supportive care guidelines. Premedication with acetaminophen and diphenhydramine prior to each dose of rituximab (or biosimilar) is strongly recommended.

Rituximab or biosimilar (RTX): IV infusion
Days: 1, 8, 15
Dose: 375 mg/m^2/dose

Special precautions: Due to the risk of hypotension, it is recommended to hold antihypertensive medications 12 hours prior to infusion.

See Section 5.0 for management of allergic and anaphylactic reactions to rituximab. Patients who cannot receive any further rituximab due to anaphylaxis or hepatitis will be taken off protocol therapy.

4.2.4 Callback (see Section 3.1.6):

A Callback must be completed by Day 22 or as soon as a patient is medically stable to proceed to the next cycle. Reasons for delays in submitting Callback should be documented in the medical chart. Patients assigned to Arm LMP-TC must start the next course of therapy within 2 weeks of the Callback.

4.2.5 Post-Induction Treatment Arm Assignment

Patients newly diagnosed with PTLD who achieve a CR after induction (RTX1) will be assigned to Arm RTX (see Section 4.3).

Patients with newly diagnosed PTLD who have a PR, SD or PD at the end of Induction (RTX1) will be assigned to Arm LMP-TC. If no suitable LMP-specific T-cell product is available, these patients will immediately be taken off protocol therapy. Chemotherapy is strongly recommended. Further therapy is as per institutional guidelines.

Following completion of Induction, the next course of therapy starts on Day 28 for Arm RTX, or within 2 weeks of the Callback for Arm LMP-TC.

4.3 Arm RTX: Course 2 of Rituximab (RTX2)

4.3.1 Course RTX2 For newly diagnosed patients in CR after Induction. Course RTX2 lasts 21 days and begins on Day 1.	_____ Patient COG ID number _____ DOB

This TDM is on 2 pages.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
Rituximab or biosimilar (RTX)	IV	375 mg/m^2/dose	1, 8, 15	Please refer to Appendix II for detailed rituximab (or biosimilar) administration guidelines including recommended premedication and monitoring during infusion.

Ht _____cm Wt _____kg BSA _____m^2

Date Due	Date Given	Day	RTX or biosimilar _____mg	Studies
			Enter calculated dose above and actual dose administered below	
		1	_____mg	a-h, j, k
		8	_____mg	d-h, k
		15	_____mg	d-h, k
		21		d-k

End of protocol therapy is after the final evaluation.

See Section 5.0 for Dose Modifications including management of infusion-related reactions, and see Section 4.1.4 for Supportive Care Guidelines.

4.3.2 Required Observations in Course RTX2

a. Height/ BSA.

b. Pregnancy Test: Female patients of childbearing potential require a negative pregnancy test prior to starting RTX2.

c. History and Physical Exam, Vital Signs, Performance Status, Weight.

d. CBC, diff.

e. Electrolytes, BUN, creatinine: for all patients on Days 1 and 21. Note: interim weekly evaluations are required only for patients with renal transplant.

f. AST, ALT, total and direct bilirubin, albumin, total protein, LDH: for all patients on Days 1 and 21. Note: interim weekly evaluations are required only for patients with liver transplant.

g. Documentation of immunosuppressive medication.

h. If applicable: tacrolimus, sirolimus, cyclosporine level. If levels are subtherapeutic, adjust dose(s) as per institutional guidelines and repeat levels approximately every 48-72 hours until the therapeutic range has been reached.

i. CT with contrast of involved areas. See Section 10.2 specifics for use of MRI or PET in addition to or as an alternative modality to CT. Patients with GI tract involvement require endoscopy with biopsies if they do not have measurable disease by imaging.

j. EBV PCR: 5 mL whole blood in EDTA (purple top). Submit specimen to BCM. See Section 15 for specimen collection and shipment instructions.

k. Correlative Biology Studies: Submission to BCM required for patients who consent for the optional studies. See Section 15 for timing and shipping instructions.

This listing only includes evaluations necessary to answer the primary and secondary aims. OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD CLINICAL CARE.

Comments
(Include any held doses, or dose modifications)

4.3.3 Course RTX2 Treatment Details

See Appendix II for rituximab infusion and Section 4.1.4 for supportive care guidelines. Premedication with acetaminophen and diphenhydramine prior to each dose of rituximab is strongly recommended.

Rituximab or biosimilar (RTX): IV infusion
Days: 1, 8, 15
Dose: 375 mg/m^2/dose

Special precaution: due to the risk of hypotension, it is recommended to hold antihypertensive medications 12 hours prior to infusion.

See Section 5.0 for management of allergic and anaphylactic reactions to rituximab. Patients who cannot receive any further rituximab due to anaphylaxis or hepatitis will be taken off protocol therapy.

4.3.4 Post RTX2 Response Assessment

Evaluation by CT with contrast should be completed during Week 3 of Course RTX2. See Section 10.2 for specific instances in which MRI or PET are recommended in addition to or as an alternative modality to CT.

Following completion of RTX2, patients have completed protocol therapy.

For patients who develop PD, chemotherapy as per institutional guidelines is strongly recommended.

4.4 Arm LMP-TC: Course LMP-TC1

4.4.1	**Course LMP-TC1** Cohort A: For newly diagnosed patients with PR, SD or PD response to Induction. Cohort B: For all relapsed patients regardless of response to rituximab. Cohort C: For all patients with refractory disease. Course LMP-TC1 therapy lasts 6 weeks and begins on Day 0	_____ Patient COG ID number _____ DOB

To start this course, patients require adequate immunosuppression: Tacrolimus level must be > 4ng/ml OR cyclosporine level must be > 100ng/ml OR sirolimus level must be > 4ng/ml OR everolimus level must > 3ng/ml. This levels MUST be maintained throughout the course.

This TDM is on 2 pages.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
LMP-specific T cells (IND: 17068)	IV over 1-2 minutes	2 x 10^7 cells/m^2/dose	0, 7	Please refer to Appendix III for detailed administration guidelines including recommended premedication and monitoring during and after infusion.
Immuno-suppression: _____ *Specify Medication*	IV/PO	_____ *Specify dose* _____ *Specify target level*	Days 0-47	See below Section 4.4.5
Immuno-suppression: _____ *Specify Medication*	IV/PO	_____ *Specify dose* _____ *Specify target level*	Days 0-47	See below Section 4.4.5

Ht _____cm Wt _____kg BSA _____m^2

Date Due	Date Given	Day	LMP-specific T Cells _____ /m^2	Immunosuppression: Drug:_____ Dose:_____ mg/dose Frequency: _____	Immunosuppression: Drug: _____ Dose:_____mg/dose_ Frequency: _____	Studies
			Enter calculated dose above and actual dose administered below	Enter medication, dose & frequency (total daily dose may be divided into one or more doses)		
		0	_____cells	_____	_____	a-i, k, l
		7	_____cells	_____	_____	d-i, l
		14		_____	_____	d-i, k, l
		21		_____	_____	d-i,
		28		_____	_____	d-i, l
		35		_____	_____	d-i
		36		_____	_____	j
		41		_____	_____	d-i, k, l

LMP-TC1 Confirmation CRF must be submitted within 24 hours of the 2nd dose (i.e. on Day 8), *OR as soon as possible after determination is made that the patient will not receive the 2nd dose.*

The end of Course LMP-TC1 response evaluation and Callback must be submitted by Day 42 (see Section 3.1.6).

See Section 5.0 for Dose Modifications including management of infusion-related reactions, and see Section 4.1.4 for Supportive Care Guidelines.

4.4.2 Required Observations in Course LMP-TC1

For Cohort C patients: All baseline studies must be performed prior to starting protocol therapy. Unless otherwise indicated, observations a-i can be performed up to 7 days prior to the start of therapy. Radiographic imaging and/or endoscopy with biopsies, bone marrows, or lumbar punctures do not need to be repeated as long as they were obtained within 14 days prior to enrollment.

a. Height/ BSA.

b. Pregnancy Test: Female patients of childbearing potential require a negative pregnancy test prior to starting LMP-TC1.

c. O_2-saturation.

d. History and Physical Exam, Vital Signs, Performance Status, Weight.

e. CBC, diff.

f. Electrolytes, BUN, creatinine: for all patients at Days 0 and 41. Note: interim weekly evaluations are required only for patients with renal transplant.

g. AST, ALT, total and direct bilirubin, albumin, total protein, LDH: for all patients at Days 0 and 41. Note: interim weekly evaluations are required only for patients with liver transplant.

h. Documentation of immunosuppressive medication.

i. As applicable: tacrolimus, cyclosporine, sirolimus and/or everolimus levels weekly. If levels are subtherapeutic as outlined above, adjust dose(s) as per institutional guidelines and repeat levels approximately every 48-72 hours until the therapeutic range has been reached. See Section 4.4.5

j. CT with contrast of involved areas: Response evaluation between Days 36-41 of Course LMP-TC1. See Section 10.2 specifics for use of MRI or PET in addition to or as an alternative modality to CT. Patients with GI tract involvement require endoscopy with biopsies if they do not have measurable disease by imaging.

k. EBV PCR: 5 mL whole Blood in EDTA (purple top). Submission to BCM required for centralized assay. See Section 15 for instructions.

l. Correlative Biology Studies: Submission to BCM required for patients who consent for the optional studies. See Section 15 for instructions.

This listing only includes evaluations necessary to answer the primary and secondary aims. OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD CLINICAL CARE.

Comments
(Include any held doses, or dose modifications)

4.4.3 Course LMP-TC1 Treatment Details

Refer to Appendix III for detailed instructions for the preparation and administration of the LMP-specific T-cell product.

LMP-specific T cells: IV infusion over 1-2 minutes
Days: 0, 7
Dose: 2 x 10^7 cells/m^2/dose

4.4.3.1 **Premedication**

30-60 minutes prior to LMP-specific T-cell infusion, premedication with acetaminophen and diphenhydramine is strongly recommended unless contraindicated.

Acetaminophen 10-15 mg/kg; max 650 mg PO 30-60 minutes prior to LMP-specific T cells. (May be given IV in exceptional circumstances.)

Diphenhydramine 1 mg/kg; max 50 mg PO 30-60 minutes prior to LMP-specific T cells (may be given IV).

4.4.3.2 **LMP-specific T Cell Product Preparation and Thawing**

LMP-specific T cells ($2x10^7$cells/m^2) will be thawed according to the SOP (see Appendix III) and administered IV 30-60 minutes after pre-medication, if applicable.

4.4.4 Post LMP-CT1 Response Evaluation

CT scan with contrast of all involved areas must be completed during Week 6 of LMP-TC1 and the Callback must be submitted by Day 42. See Section 10.2 specifics for use of MRI or PET in addition to or as an alternative modality to CT.

1) Patients with CR at the end of LMP-TC1 have completed protocol therapy and will transition to follow-up.
2) Patients with PR or SD at the end of LMP-TC1 who have a suitable LMP-specific T-cell product available are eligible for Course LMP-TC2.
3) Patients with PR and SD who do not have a suitable LMP-specific T-cell product available, or patients with PD at the end of LMP-TC1 will go off protocol therapy. Chemotherapy is strongly recommended. Further treatment is according to institutional guidelines.

4.4.5 Immunosuppression

Unlike chemotherapy, LMP T cells do NOT provide any immunosuppression. Patients assigned to Arm LMP-TC are required to have minimum levels of either calcineurin inhibitors and/or MTOR inhibitors at the start of the course and must maintain these minimum levels throughout the course. To prevent organ rejection, compliance with the below guidelines is required.

MINIMUM Levels for Calcineurin inhibitors:
Tacrolimus 4 ng/ml
Cyclosporine 100 ng/ml

MINIMUM Levels for MTOR Inhibitors:
Sirolimus 4 ng/ml

Everolimus 3 ng/ml
For patients on combination therapy, the minimum level needs to be maintained at least for the calcineurin inhibitors.

Course LMP-TC2 will start as soon as a suitable LMP-specific T-cell product is available but no later than 21 days from the end of LMP-TC1.

See Section 5.0 for Dose Modifications including management of infusion-related reactions.

4.5 Arm LMP-TC: Course LMP-TC2

4.5.1 Course LMP-TC2 For patients with PR or SD following Course LMP-TC1. Course LMP-TC1 therapy lasts 6 weeks and begins on Day 0.	_____ Patient COG ID number _____ DOB

Course LMP-TC2 will start as soon as a suitable LMP-specific T-cell product is available but no later than 21 days from the end of LMP-TC1. To start this course, patients require adequate immunosuppression: Tacrolimus level must be > 4ng/ml OR cyclosporine level must be > 100ng/ml OR sirolimus level must be > 4ng/ml OR everolimus level must > 3ng/ml. This levels MUST be maintained throughout the course. This TDM is on 2 pages.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
LMP-specific T cells (IND: 17068)	IV over 1-2 minutes	2 x 10^7 cells/m^2/dose	0, 7	Please refer to Appendix III for detailed administration guidelines including recommended premedication and monitoring during and after infusion.
Immuno-suppression: _____ _____ *Specify Medication*	IV/PO	_____ *Specify dose* _____ *Specify target level*	Days 0-47	See below Section 4.5.5
Immuno-suppression: _____ *Specify Medication*	IV/PO	_____ *Specify dose* _____ *Specify target level*	Days 0-47	See below Section 4.4.5

Ht _____ cm Wt _____ kg BSA _____ m^2

Date Due	Date Given	Day	LMP-specific T Cells _____ /m^2	Immunosuppression: Drug:_____ Dose:_____ mg/dose Frequency: _____	Immunosuppression: Drug:_____ Dose:_____ mg/dose Frequency: _____	Studies
			Enter calculated dose above and actual dose administered below	Enter medication, dose & frequency (total dose may be divided into one or more daily doses)		
		0	_____ cells	_____	_____	a-i, k ,l
		7	_____ cells	_____	_____	d-i
		14		_____	_____	d-i, k
		21		_____	_____	d-i
		28		_____	_____	d-i
		35		_____	_____	d-i
		41		_____	_____	d-k

*After LMP-TC1 Correlative Biology Study dates are calculated from LMP-TC1 Day 0. The Week 8 and Month 3 time points are likely to occur during Course LMP-TC2. Day may vary. See Section 15.3.3 for additional detail.

End of protocol therapy is after the final evaluation.

See Section 5.0 for Dose Modifications including management of infusion-related reactions, and see Section 4.1.4 for Supportive Care Guidelines.

4.5.2 Required Observations in Course LMP-TC2

a. Height/ BSA.

b. Pregnancy Test: Female patients of childbearing potential require a negative pregnancy test prior to starting LMP-TC2.

c. O_2-saturation.

d. History and Physical Exam, Vital Signs, Performance Status, Weight.

e. CBC, diff.

f. Electrolytes, BUN, creatinine: for all patients at Days 0 and 41. Note: interim weekly evaluations are required only for patients with renal transplant.

g. AST, ALT, total and direct bilirubin, albumin, total protein, LDH: for all patients at Days 0 and 41. Note: interim weekly evaluations are required only for patients with liver transplant.

h. Documentation of immunosuppressive medication.

i. As applicable: tacrolimus, cyclosporine, sirolimus and/or everolimus levels weekly. If levels are subtherapeutic, adjust dose(s) as per institutional guidelines and repeat levels approximately every 48-72 hours until the therapeutic range has been reached. See Section 4.5.5

j. CT with contrast of involved areas: response evaluation between Days 36-41 of LMP CTL2. See Section 10.2 specifics for use of MRI or PET in addition to or as an alternative modality to CT. Patients with GI tract involvement require endoscopy with biopsies if they do not have measurable disease by imaging.

k. EBV PCR: 5 mL whole Blood in EDTA (purple top). Submission to BCM required for centralized assay. See Section 15 instructions.

l. Correlative Biology Studies: Submission to BCM required for patients who consent for the optional studies. See Section 15 for instructions.

This listing only includes evaluations necessary to answer the primary and secondary aims. OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD CLINICAL CARE.

Comments
(Include any held doses, or dose modifications)

4.5.3 Course LMP-TC2 Treatment Details

Refer to Appendix III for detailed instructions for the preparation and administration of LMP-specific T cells.

LMP-specific T cells: IV infusion over 1-2 minutes
Days: 0, 7
Dose: 2 x 10^7 cells/m^2/dose

4.5.3.1 **LMP-TC2 LMP-specific T cells**

Course LMP-TC2 doses will come from the original infused product used in LMP-TC1 if the patient had a PR and sufficient vials are available.

If the patient had SD and/or there are insufficient cells in the original product, another LMP-specific T-cell product may be selected and shipped (per SOP) for Course LMP-TC2 if an additional suitably matched product is available.

4.5.3.2 **Premedication**

30-60 minutes prior to LMP-specific T-cell infusion, premedication with acetaminophen and diphenhydramine is strongly recommended unless contraindicated.

Acetaminophen 10-15 mg/kg; max 650 mg PO 30-60 minutes prior to LMP-specific T cells. (May be given IV in exceptional circumstances.)

Diphenhydramine 1 mg/kg; max 50 mg PO 30-60 minutes prior to LMP-specific T cells (may be given IV).

4.5.3.3 **LMP-specific T Cell Product Preparation and Thawing**

LMP-specific T cells ($2x10^7$cells/m^2) will be thawed according to the SOP (see Appendix III) and administered IV 30-60 minutes after pre-medication, if applicable.

4.5.4 Post-therapy Response Assessment

Evaluation by CT scan with contrast of all involved areas should be completed during Week 6 of LMP-TC2. See Section 10.2 specifics for MRI or PET in addition to or as an alternative modality to CT. Note: for patients with PR, SD or PD, chemotherapy is strongly recommended. Further treatment is according to institutional guidelines.

4.5.5 Immunosuppression

Unlike chemotherapy, LMP T cells do NOT provide any immunosuppression. Patients assigned to Arm LMP-TC are required to have minimum levels of either calcineurin inhibitors and/or MTOR inhibitors at the start of the course and must maintain these minimum levels throughout the course. To prevent organ rejection, compliance with the below guidelines is required.

MINIMUM Levels for Calcineurin inhibitors:
Tacrolimus 4 ng/ml
Cyclosporine 100 ng/ml

MINIMUM Levels for MTOR Inhibitors:
Sirolimus 4 ng/ml
Everolimus 3 ng/ml

For patients on combination therapy, the minimum level needs to be maintained at least for the calcineurin inhibitors.

See Section 5.0 for Dose Modifications including management of infusion-related reactions.

5.0 DOSE MODIFICATIONS FOR TOXICITIES

5.1 Modifications Due to Hepatitis B or C Infection

Any patients with evidence of hepatitis B or C infection must have rituximab (or biosimilar) discontinued and must be taken off protocol therapy if they are undergoing treatment in Induction or Course RTX2.

5.2 Management of Rituximab (or biosimilar) Infusion-related reactions

During the infusion of rituximab (or biosimilar), the occurrence of fever and chills and/or hypotension is possible as well as other infusion related symptoms. In case of these adverse events, the rituximab (or biosimilar) infusion must be interrupted and the patient treated appropriately as per institutional guidelines. After the symptoms have subsided, the infusion may be restarted at half the initial infusion rate per guidelines in Appendix II.

Patients with repeated allergic or anaphylactic reaction after more than 1 dose of rituximab (or biosimilar) should have rituximab (or biosimilar) discontinued at the investigator's discretion according to institutional guidelines. Patients who do not tolerate all doses of rituximab (or biosimilar) will be taken off protocol therapy and further therapy is at the treating physician's discretion.

5.3 Management of LMP-specific T Cells Infusion-related Reactions

LMP-specific T cells have been well tolerated in preliminary studies but carry the risk of causing an allergic or anaphylactic reaction. Emergency medications including diphenhydramine, acetaminophen, hydrocortisone or methylprednisolone and epinephrine should be readily available during the infusion. Infusion should be monitored by medical staff competent in managing anaphylaxis. In case of any adverse events, the LMP-specific T-cell infusion must be interrupted and the patient treated appropriately as detailed in Appendix III.

Patients who develop allograft rejection and/or failure possibly, probably or definitely related to LMP-TC will not receive any further LMP-TC and will be taken off protocol therapy. Further therapy is at the treating physician's discretion. Administration of high dose steroids may be considered since steroid doses of > 0.5 mg/kg/day can effectively eliminate LMP-specific T cells in vivo.

Patients who develop Grade 3 or higher GvHD will not receive any further LMP-TC therapy and will be taken off protocol therapy.

6.0 AGENT INFORMATION

6.1 ALLOGENEIC LATENT MEMBRANE PROTEIN SPECIFIC T-LYMPHOCYTES (LMP-specific T cells) NSC# 782666, [redacted] **(04/29/16)**

[redacted]

[redacted]

[redacted]

Participating clinical trial sites should also consult with their local Institutional Biosafety Committee (IBC) for site-specific recommendations regarding preparation, handling and disposal; healthcare worker precautions; and patient care.

6.2 RITUXIMAB, RITUXIMAB-ABBS (07/30/19)

(Rituxan®, Truxima®, Biogen-IDEC-C2B8) NSC #687451

6.2.1 Source and Pharmacology

Rituximab is a genetically engineered chimeric murine/human monoclonal antibody which binds specifically to the antigen CD20 (human B lymphocyte restricted differentiation antigen, Bp35) located on the surface of pre B and mature B lymphocytes of both normal and malignant cells. The antibody is an IgG_1 kappa immunoglobulin containing murine light- and heavy-chain variable region sequences and human constant region sequences. Rituximab is composed of two heavy chains of 451 amino acids and two light chains of 213 amino acids and has an approximate molecular weight of 145 kD. It is produced in mammalian cell (Chinese Hamster Ovary) culture.

CD20 regulates an early step(s) in the activation process for cell cycle initiation and differentiation, and possibly functions as a calcium ion channel. Rituximab binds to the CD20 antigen on B lymphocytes and recruits immune effector functions to mediate B-cell lysis. Possible mechanisms of cell lysis include complement-dependent cytotoxicity and antibody-dependent cell mediated cytotoxicity. The antibody has been shown to induce apoptosis in the DHL-4 human B-cell lymphoma line.

In 83% of patients, circulating B cells were depleted within the first three doses of rituximab with sustained depletion for up to 6 to 9 months post-treatment. Serum levels and half-life are proportional to the dose and have ranged from 31.5 to 152.6 hours after the first infusion and 83.9 to 407 hours after the fourth weekly infusion of 375 mg/m^2. The wide range of half-lives may reflect the variable tumor burden among patients and the changes in CD20-positive (normal and malignant) B-cell populations upon repeated administrations.

6.2.2 Toxicity

Incidence	Toxicities
Common (> 20% of patients)	• Infusion reactions • Infections • Lymphopenia • Fever • Chills • Fatigue • Nausea
Occasional (4-20% of patients)	• Diarrhea, vomiting • Neutropenia • Leukopenia • Anemia • Thrombocytopenia • Night sweats • Rash, pruritus, urticaria • Increased cough • Rhinitis

	• Bronchospasm, dyspnea • Headache • Pain • Myalgia, arthralgia • Throat irritation • Flushing • Hypotension • Hypertension • Hypogammaglobulinemia
Rare (≤ 3% of patients)	• Severe mucocutaneous reactions (paraneoplastic pemphigus, Stevens-Johnson syndrome, lichenoid dermatitis, vesiculobullous dermatitis, and toxic epidermal necrolysis) • Hepatitis B reactivation with fulminant hepatitis • Tumor lysis syndrome • Renal toxicity • Cardiac adverse reactions, including ventricular fibrillation, myocardial infarction, and cardiogenic shock • Antibody formation • Bowel obstruction and perforation • Bronchiolitis obliterans, interstitial lung disease • Posterior Reversible Encephalopathy Syndrome (PRES) / Reversible Posterior Leukoencephalopathy Syndrome (RPLS) • Prolonged pancytopenia, marrow hypoplasia
Pregnancy & Lactation	Based on human data, rituximab products can cause fetal harm due to B-cell lymphocytopenia in infants exposed in-utero. Advise pregnant women of the risk to a fetus. Females of childbearing potential should use effective contraception while receiving rituximab products and for 12 months following the last dose of a rituximab product. It is unknown whether the drug is excreted in breast milk; however, human IgG is excreted in human milk. Advise women not to breastfeed during treatment with rituximab products and for 6 months after the last dose.

6.2.3 Formulation and Stability

Rituxan® is a sterile, clear, colorless, preservative free liquid concentrate for intravenous administration. Rituximab is supplied at a concentration of 10 mg/mL in either 100 mg (10 mL) or 500 mg (50 mL) single use vials. The product contains 9 mg/mL sodium chloride, 7.35 mg/mL sodium citrate dihydrate, 0.7 mg/mL polysorbate 80, and SWFI. The pH is adjusted to 6.5. Store refrigerated at temperatures of 2°-8°C (36°-46°F). Protect from direct sunlight.

Truxima® is a clear to opalescent, colorless to pale yellow solution for intravenous infusion supplied at a concentration of 10 mg/mL in either 100 mg/10 mL or 500 mg/50 mL single-dose vials. Each mL of solution contains 10 mg rituximab-abbs, polysorbate 80 (0.7 mg), sodium chloride (9 mg), tri-sodium citrate dihydrate (7.35 mg), and Water for Injection, USP. The pH is 6.5. Truxima® solutions do not contain a preservative, hence diluted solutions should be stored refrigerated (2°C

to 8°C). No incompatibilities between Truxima® and polyvinylchloride or polyethylene bags have been observed.

6.2.4 Guidelines for Administration

See Treatment and Dose Modifications sections of the protocol for additional detail. See Appendix II for rituximab infusion guidelines.

Dilute to a final concentration of 1 to 4 mg/mL in NS or D5W. Rituximab solutions for infusion may be stored at 2º-8°C (36º-46°F) for 24 hours and have been shown to be stable for an additional 24 hours at room temperature.
DO NOT ADMINISTER AS AN INTRAVENOUS PUSH OR BOLUS. Premedications consisting of acetaminophen and H1-receptor antagonist should be administered prior to each infusion. Since transient hypotension may occur during rituximab infusions, consider withholding antihypertensive medications 12 hours prior to infusion.

6.2.5 Supplier

Commercially available from various manufacturers. See package insert for further information.

7.0 EVALUATIONS/MATERIAL AND DATA TO BE ACCESSIONED

Timing of protocol therapy administration, response assessment studies, and surgical interventions are based on schedules derived from the experimental design or on established standards of care. Minor unavoidable departures (up to 72 hours) from protocol directed therapy and/or disease evaluations (and up to 1 week for surgery) for valid clinical, patient and family logistical, or facility, procedure and/or anesthesia scheduling issues are acceptable (except where explicitly prohibited within the protocol).

7.1 End of Therapy & Follow-up

7.1.1 Arm RTX

End of therapy is Day 22 of Course RTX2 after the CT scan to evaluate response.

7.1.2 Arm LMP-TC

End of therapy is Day 42 of Course LMP-TC1 for patients with a CR or PD after this course and for patients with PR or SD after this course who do not have a suitable T-cell product available for Course LMP-TC2.

End of therapy is Day 42 of Course LMP-TC2 for all other patients.

7.1.3 Observations During Follow-up

Observations During Follow-up After Completion of Therapy	1 Months	2 Months	3 Months	6 Months	9 Months	12 Months
History and Physical exam	X	X	X	X	X	X
Performance status	X	X	X	X	X	X
Documentation of immunosuppressive medication	X	X	X	X	X	X
If applicable tacrolimus, sirolimus, cyclosporine level	X	X	X	X	X	X
CBC, diff	X	X	X	X	X	X
Electrolytes, BUN, creatinine	X	X	X	X	X	X
AST, ALT, total and direct bilirubin, albumin, total protein, LDH	X	X	X	X	X	X
CT* of involved areas	As needed for clinical symptoms					
Endoscopy of involved areas	As needed for clinical symptoms					
Specimens for Submission to BCM See Section 15 for Details						
EBV PCR (Required for all patients): 5 mL whole Blood in EDTA (purple top)	X	X	X	X	X	X
Correlative biology studies (for patients consenting for the optional studies)	Arm LMP-TC follow-up time points are calculated from Day 0 of LMP-TC1 regardless of LMP-TC2 participation. **See Section 15** For a detailed guide to the follow-up sampling time points.					

* And/or MRI, PET. The same method of assessment and the same technique should be used at baseline and during follow-up. See Section 10.2.

See COG Late Effects Guidelines for recommended post treatment follow-up: http://www.survivorshipguidelines.org/

Note: Follow-up data are expected to be submitted per the Case Report Forms (CRFs) schedule.

7.2 Biology Research Studies

This section is provided as a brief overview of required and optional biology studies. See Section 15 for a detailed guide for time points, specimen requirements and shipping instructions.

Study		Before or During Induction	During Course RTX2	After Course RTX2	During Course LMP-TC1	After Course LMP-TC1	In Case of CRS	In Case of Allograft Rejection or Failure
Required	EBV PCR	**X**	**X**	**X**	**X**	**X**		
Optional	General immune reconstitution		**X**	**X**	**X**	**X**	**X**	
	Persistence of LMP-specific T cells		**X**	**X**	**X**	**X**		**X***
	Immunity to EBV		**X**	**X**	**X**	**X**		
*Submission only in case of suspected allograft rejection or failure during Course LMP-TC1 or LMP-TC2. Obtain specimen prior to increasing immunosuppression or commencing steroid therapy.								

8.0 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

8.1 Criteria for Removal from Protocol Therapy

a) Repeat eligibility studies (if required) are outside the parameters required for eligibility (see Section 3.2.).
b) Pregnancy.
c) Evidence of Hepatitis B or C infection during any course of treatment with rituximab (or biosimilar).
d) Unacceptable toxicity due to protocol therapy (See Section 5.2 and Section 5.3).
e) Progressive disease after or during Course RTX2, Course LMP-TC1, Course LMP-TC2.
f) Assigned to Arm LMP-TC without an available matched LMP-specific T-cell product.
g) Assigned to Arm LMP-TC without HLA typing available by the Day 22 post-induction Callback.
h) Refusal of further protocol therapy by patient/parent/guardian.
i) Physician determines it is in the patient's best interest.
j) Development of a second malignancy.
k) Completion of planned protocol therapy.
l) Inability to attain and maintain therapeutic immunosuppressive drug levels on the LMP TC arm

Patients who are off protocol therapy are to be followed until they meet the criteria for Off Study (see below). Follow-up data will be required unless patient is taken off study.

8.2 Off Study Criteria

a) Death.
b) Lost to follow-up.
c) Patient enrollment onto another COG study with tumor therapeutic intent (e.g., at recurrence).
d) Withdrawal of consent for any further data submission.
e) The fifth anniversary of the date the patient was enrolled on this study.
f) No treatment received.

9.0 STATISTICAL CONSIDERATIONS

9.1 Sample Size and Study Duration

Review of patient accrual onto recent phase 2 PTLD studies and personal communication from Canadian investigators indicates the following entry rates can be expected:

Disease Group	Patients/Year
Post-Transplant Lymphoproliferative Disorder (PTLD)	19

The study will likely require 3.1 to 4.9 years to enroll sufficient patients to evaluate LMP-specific T cells in the stated disease group. A maximum of 90 eligible patients is anticipated to obtain at least 30 patients evaluable for the primary endpoint.

Patients in Cohort A (newly diagnosed) are assigned to Arm LMP-TC only if they fail to achieve a CR after Course RTX1, while patients in Cohorts B (relapsed) and C (refractory) are automatically assigned to Arm LMP-TC. To avoid going too far past the targeted sample size of 30 patients evaluable for the primary aim (i.e., assigned to Arm LMP-TC) while avoiding the need to repeatedly open and close the trial to enrollments, we will closely monitor enrollments when the number of patients assigned to Arm LMP-TC approaches 30. The number of available enrollments will be limited to the smallest number such that there is a 90% chance of reaching 30 patients assigned to Arm LMP-TC assuming each patient in Cohort A has a 40% chance of being assigned to Arm LMP-TC and all patients in Cohort B and C will be assigned to Arm LMP-TC. If at any time the number of patients enrolled in Cohort A but not having reached Callback equals or exceeds this threshold, the study will be closed to accrual until all patients currently enrolled have either been assigned to either Arm RTX or Arm LMP-TC or have been removed from protocol therapy. If after that there are fewer than 30 patients assigned to Arm LMP-TC, the study will be re-opened with the number of available slots as in the table below.

The table below displays the maximum number patients that will be allowed to be enroll, the probability of reaching 30 patients on Arm LMP-TC if there are exactly that many patients in Cohort A pre-Callback, and the probability of exceeding 36 patients on Arm LMP-TC if there are exactly that many patients in Cohort A pre-Callback.

Current Cohort A patients assigned to Arm LMP-TC plus all patients in Cohorts B and C	Maximum number of Cohort A patients pre-Callback	Probability of reaching 30 patients on Arm LMP-TC	Probability of exceeding 36 patients on Arm LMP-TC
21	30	90.6%	9.7%
22	27	90.5%	7.4%
23	24	90.4%	5.3%
24	21	90.4%	3.5%
25	18	90.6%	2.0%
26	15	90.9%	0.9%
27	12	91.7%	0.3%
28	9	92.9%	<0.1%
29	5	92.2%	—

9.2 Study Design

The primary endpoint of the study (Aim 1.1.1) is the percentage of patients assigned to Arm LMP-TC who had a suitable LMP-specific T-cell product, were treated within two weeks of the expected start date (Callback for Cohorts A and B, study enrollment for Cohort C), and received both weekly doses in a cooperative multi-institutional setting. All 3 Cohorts will be analyzed together for the primary aim.

The main secondary endpoint of the study (Aim 1.2.1) is the percentage of all eligible patients who had a suitable LMP-specific T-cell product derived from a Third Party LMP-specific T-cell bank available in a cooperative multi-institutional setting. Additional secondary endpoints (Aims 1.2.2-1.2.8) will be the estimation of progression-free survival (PFS), event-free survival (EFS), overall survival (OS), response rate (RR), and toxicity rates in the study population.

At least thirty (30) patients evaluable for the primary endpoint will be enrolled, with a futility analysis after 15 patients. The study will be considered successful if 23/30 evaluable patients in the trial are matched, are treated within two weeks of the expected start date, and receive both weekly doses of LMP-specific T cells. If exactly 23/30 successes occurred, the one-sided exact binomial 95% confidence interval (adjusted for the interim analysis by the method of Jung and Kim)[37] would be $p > 60.7\%$, which would exclude the possibility that the true success rate is as low as 60%. If the true success rate in the study population is 80%, then the proposed sample size of 30 will give 75.3% power to get at least 23/30 successes. If the true success rate in the study population is 60%, then there is a 4.2% chance of getting at least 23/30 successes.

Since evaluability for the primary endpoint depends on the response to the initial treatment with rituximab for patients in Cohort A (newly diagnosed patients), it is possible that more than 30 patients will be evaluable for the primary endpoint. In that case, the trial will be considered successful if the one-sided exact binomial 95% confidence interval excludes the possibility that the true success rate is as low as 60%. The required number of successes and power under various scenarios is displayed below.

Number of evaluable patients	Number of successes needed	Power (80% true rate)	Power (60% true rate)
30	23	75.3%	4.2%
31	24	72.4%	3.2%
32	25	69.3%	2.4%
33	25	78.7%	4.2%
34	26	76.2%	3.3%
35	27	73.5%	2.5%
36	27	81.4%	4.2%

9.3 Methods of Analysis

For the primary endpoint, the point estimate of the proportion successfully matched and treated (among all 3 Cohorts combined) will be the uniformly minimum variance unbiased estimator, and an exact one-sided binomial 95% confidence interval (adjusted for the interim analysis by the method of Jung and Kim)[37] will be used to get a lower bound for the actual rate of successful treatments as defined in the primary objective.

For the secondary endpoints:

- The proportion of eligible patients who are successfully matched will be assessed using the uniformly minimum variance unbiased estimator for the proportion and an exact one-sided binomial 95% confidence interval (adjusted for the interim analysis by the method of Jung and Kim)[37] to get a lower bound for the actual rate.
- PFS (defined as time to first occurrence of progression or death (events) or loss to follow-up or survival to analysis date (non-events)), EFS (defined as time to first occurrence of relapse, second/secondary malignant neoplasm (SMN), death (events) or loss to follow-up or survival to analysis date (non-events)), and OS (defined as time to death (event) or loss to follow-up or survival to analysis date (non-events)) will be assessed using Kaplan-Meier estimates, both for all patients combined and also separately in each Cohort. Aim 1.2.8 will be assessed using the Log-Rank test for EFS and OS and the exact conditional test of proportions (Fisher's Exact test) for RR, both for all patients combined and stratified by Cohort.
- Response rates will be assessed using exact two-sided binomial 95% confidence intervals to get estimates of the response rate. Aim 1.2.2 will be evaluated in Cohorts A and B only (combined and separately), with response classified by comparing disease evaluation at the Week 3 evaluation to the baseline of disease evaluation at study entry using the criteria in Section 10.2. Patients with CR will be considered responders. For Aim 1.2.5, response will be classified by comparing disease evaluation at the Week 6 of LMP-CT1 evaluation to the baseline of disease evaluation at the Week 3 evaluation using the criteria in Section 10.2, both in all Cohorts combined and in each Cohort separately. Patients with CR or PR will be considered responders.
- Toxicities will be described using descriptive statistics. Toxicity monitoring and analysis will be performed based on "as treated".

We will assess the proportion of successes for the primary aim on the first 15 patients assigned to Arm LMP-TC as an interim futility monitoring rule. If fewer than 10 of the first 15 patients are successes for the primary aim (matched and treated within the prescribed timeframe), the Study Committee will assess the reasons for failure and may choose to close the study if it is felt that the reasons are not correctable. If the true success rate is 60%, this rule will be invoked with probability 59.7%; if the true success rate is 80%, the rule will be invoked with probability 6.1%.

We will do real-time monitoring for progression rate at week 10 and for certain protocol-specific toxicities, namely: allograft failure, allograft rejection, cytokine release syndrome grade 3 or higher, and graft versus host disease (see Appendix V). The monitoring will be done using Bayesian rules with beta priors.[38,39] The four parameters for each scenario are the two beta distribution parameters (α, β), the unacceptable probability rate for the event we are monitoring (p_0), and the posterior probability that the actual rate exceeds p_0 ($P(p > p_0 \mid \text{Data})$), which is calculated using the standard Bayesian posterior probability formula

$$P(p > p_0 \mid \text{Data}) = \frac{\int_{p_0}^{1} \binom{n}{x} p^x (1-p)^{n-x} \frac{\Gamma(\alpha+\beta)}{\Gamma(\alpha)\Gamma(\beta)} p^{\alpha-1}(1-p)^{\beta-1}\, dp}{\int_{0}^{1} \binom{n}{x} q^x (1-q)^{n-x} \frac{\Gamma(\alpha+\beta)}{\Gamma(\alpha)\Gamma(\beta)} q^{\alpha-1}(1-q)^{\beta-1}\, dq},$$

where n is the number of observations and x is the number of events among those n observations.

We will suspend enrollment to the study if any patient suffers or is suspected to suffer allograft failure or allograft rejection to review the circumstances of the failure or rejection. A recommendation to re-open enrollment might be made if causes other than study therapy were thought to be the primary cause of failure or rejection.

For cytokine release syndrome and graft versus host disease, the analytic unit for monitoring for protocol-specific toxicities will be the patient-course. Each course where the patient receives the agent or where a protocol-specific toxicity event is observed will be considered in the analysis. We will assume a beta prior distribution with $\alpha = 0.6$ and $\beta = 1.4$ and an unacceptable toxicity rate of $p_0 = 30\%$. At least once per month, we will calculate the posterior probability (given the data) that the probability of protocol-specific toxicity exceeds the 30% threshold, *i.e.*, $P(p > 0.3 \mid \text{Data})$. If there is a posterior probability of 80% that the toxicity rate is at least 30%, then accrual will be suspended pending review by DSMC. Examples of situations in which this rule will indicate protocol-specific toxicities have been noted and are presented below:

Number of failures	Number of patient-cycles
2	3
3	6
4	8
5	11
6	14
7	17
8	20
9	23
10	26
11	29
12	32
13	35
14	38

Interim monitoring will also be performed to watch for a 20% progression rate at week 10 in newly-diagnosed patients and a 40% progression rate at week 10 for relapsed and refractory patients. For newly-diagnosed patients, the beta parameters will be $\alpha = 0.52$ and $\beta = 2.08$; and for relapsed and refractory patients the beta parameters will be $\alpha = 1.04$ and $\beta = 1.56$; if there is a posterior probability of 80% that the progression rate at week 10 is at least 20% for newly-diagnosed patients or 40% for relapsed/refractory patients, then accrual for the respective cohort or cohorts will be suspended pending review by the DSMC. The stopping rule will be triggered as described in the following table:

Number of failures	Number of newly-diagnosed patients	Number of relapsed/refractory patients
2	4	2
3	8	4
4	12	6
5	16	8

6	20	11
7	24	13
8	29	15
9	33	17
10	38	19

9.4 Evaluability for Response

Eligible patients assigned to Arm LMP-TC will be considered evaluable for the primary endpoint (percentage successfully matched and treated). All 3 Cohorts will be combined into a single set of patients for the analysis.

All eligible patients will be evaluable for Aims 1.2.1, 1.2.8, and 1.3.2. For Aim 1.2.1, all patients who submit HLA typing by the end of the trial will be evaluable, regardless of the timing of the submission.

Any eligible patient who receives at least one dose of RTX will be considered evaluable for Aims 1.2.2–1.2.4 and 1.2.6.

Any eligible patient who receives at least one dose of LMP-specific T cells will be considered evaluable for Aims 1.2.5, 1.2.7, 1.3.1, and 1.3.3.

9.5 Evaluability for Toxicity

A patient will be considered for toxicity monitoring if the patient is eligible, receives at least one dose of protocol therapy, and one of the following occurs: (1) completes a full cycle of therapy with no toxicities; (2) dies on protocol therapy for a reason considered possibly, probably, or likely related to protocol therapy; or (3) experiences an adverse experience possibly, probably, or likely related to one of the agents. A toxicity-evaluable patient will be considered in the analysis during the interval from study enrollment until protocol therapy is terminated or a toxicity-event is observed, whichever occurs first. A toxicity-evaluable patient will be considered to have experienced a protocol-specific toxicity event if: (1) the patient dies on protocol therapy for a reason considered possibly, probably, or likely related to protocol therapy; or (2) experiences a dose-limiting toxicity.

9.6 Gender and Minority Accrual Estimates

The gender and minority distribution of the study population is expected to be:

DOMESTIC PLANNED ENROLLMENT REPORT					
Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	0	1	0	0	1
Asian	0	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	7	3	0	0	10
White	16	32	3	3	54
More Than One Race	0	0	0	0	0
Total	23	36	3	3	65

INTERNATIONAL (including Canadian participants) PLANNED ENROLLMENT REPORT					
Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	0	1	0	0	1
Asian	0	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	3	1	0	0	4
White	6	12	1	1	20
More Than One Race	0	0	0	0	0
Total	9	14	1	1	25

This distribution was derived from patients enrolled on ANHL0221, the most recent COG study of PTLD.

9.7 Correlative Studies

We will summarize the *in vivo* measurements of virus-specific T cells over the pre-LMP-specific T cells to the post-LMP-specific T cells monitoring period in patients who receive LMP-specific T cells versus patients who do not to assess the pattern and magnitude of T-cell expansion and persistence for EBV and response to LMP-specific T cells administration using plots generated for each patient to graphically illustrate the pattern and duration of LMP-specific T-cell persistence and expansion. The area under the curve (AUC) will be calculated for each subject by the trapezoidal rule. The AUCs will be summarized, and after logarithmic transformation, will be analyzed by a two-sample *t*-test. Measurements of immunity, tetramer analysis and functional assays will be evaluated by descriptive statistics (means, standard deviations, medians and ranges) at each time point and analyzed by paired *t*-tests to compare changes from pre- to post-infusion.

10.0 EVALUATION CRITERIA

10.1 Common Terminology Criteria for Adverse Events (CTCAE)

This study will utilize version 5.0 of the CTCAE of the National Cancer Institute (NCI) for toxicity and performance reporting. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm). Additionally, toxicities are to be reported on the appropriate case report forms.

Please note: 'CTCAE v5.0' is understood to represent the most current version of CTCAE v5.0 as referenced on the CTEP website (i.e., v5.02 and all subsequent iterations prior to version 6.0).

10.2 Response Criteria

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Pediatric Non-Hodgkin Lymphoma Criteria[40], with modification from the Lugano classification for all patients with measurable disease.[41] Patients with evaluable disease of the GI tract will have to be evaluated by endoscopy and biopsies.

10.2.1 Induction: RTX for all non-refractory patients

For the purposes of this study, patients will be evaluated for response Week 3 of Induction (RTX1).

10.2.2 Arm RTX

In addition to a baseline scan or endoscopy with biopsies, confirmatory scans and/or endoscopy with biopsies should also be obtained at the end of Course RTX2.

10.2.3 Arm LMP-TC

In addition to a baseline scan and/or endoscopy with biopsies, additional scans and/or endoscopy with biopsies to document response need to be obtained at the end of Course LMP-TC1 during Week 6 of that course. For patients assigned to Course LMP-TC2, there will be an additional evaluation time point with scans scheduled at week 6 of LMP-TC2.

For patients found to have progressive disease (PD) at either one of those evaluations, it is recommended to repeat scans in a 2-4 week time frame as per the Lugano classification[41] to confirm progressive disease prior to changing therapy because inflammatory responses to LMP-specific T cells have been reported with a corresponding initial increase in size and metabolic uptake of involved lymph nodes.

10.2.4 Definitions

10.2.4.1 Evaluable for toxicity: A patient will be considered for toxicity monitoring if the patient is eligible and one of the following occurs: (1) completes one course of protocol therapy; (2) dies on protocol therapy for a reason considered possibly, probably, or likely related to protocol therapy; or (3) is removed from protocol therapy because of an adverse

experience possibly, probably, or likely related to one of the agents.

10.2.4.2 Evaluable for objective response: Only those patients who have measurable disease present at baseline and have received at least one dose of protocol therapy will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of Course 1 will also be considered evaluable.)

10.2.5 Disease Parameters

10.2.5.1 Measurable disease: A measurable node must have an LDi (longest diameter) greater than 1.5 cm. A measurable extranodal lesion should have an LDi greater than 1.0 cm. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

10.2.5.2 Non-measured disease: All other lesions (including nodal, extranodal, and assessable disease) should be followed as nonmeasured disease (e.g., cutaneous, GI, bone, spleen, liver, kidneys, pleural or pericardial effusions, ascites).

10.2.5.3 Target lesions: For patients staged with CT, up to six of the largest target nodes, nodal masses, or other lymphomatous lesions that are measurable in two diameters (longest diameter [LDi] and shortest diameter) should be identified from different body regions representative of the patient's overall disease burden and include mediastinal and retroperitoneal disease, if involved.

10.2.6 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 2 weeks prior to the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

10.2.6.1 Clinical lesions: Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥ 10 mm diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

10.2.6.2 Conventional CT and MRI: The major response designations will be established by CT or MRI of involved sites in conjunction with morphologic evaluation of bone marrow (BM) if involved at diagnosis. With growing concerns about the risks of cumulative ionizing radiation exposure to children from CT, MRI could be considered as an alternative

to CT for evaluating non-pulmonary disease sites. e.g., assessment of abdominal/pelvic disease. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the response guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Pulse sequences should include at a minimum, axial and coronal fat-saturated FRFSE-T2, coronal T1 and axial and coronal post-gadolinium fat-saturated T1 weighted imaging. Body scans should be performed with breath-hold scanning techniques, if possible.

10.2.6.3 PET-CT: At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for International Pediatric Non-Hodgkin Lymphoma Response Criteria measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data, which may bias an investigator if it is not routinely or serially performed.

10.2.6.4 Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

10.2.6.5 Endoscopy, Laparoscopy: Endoscopy may be used in patients with evaluable disease of the GI tract to confirm complete pathological response by obtaining biopsies.

10.2.6.6 Tumor markers: There will be no use of tumor markers to assess response in the protocol. EBV qPCR of peripheral blood PBMCs will be performed centrally to measure the presence of active viral replication and disease activity but results will not be used to stratify assignment to treatment arms.

10.2.6.7 FDG-PET: For patients with a positive PET scan at diagnosis, PET can be used to follow response in addition to a CT scan using the International Pediatric Non-Hodgkin Lymphoma Response Criteria.[40]

10.2.7 Response Criteria

10.2.7.1 Evaluation of Measurable Disease

Complete Response (CR): *Disappearance of all disease.* CT or MRI should be free of residual mass or evidence of new disease. FDG-PET should be negative.

CR unconfirmed (Cru): Residual mass is negative by FDG-PET; no new lesions by imaging examination; no new and/or progressive disease elsewhere

Partial Response (PR): 50% decrease in SPD (the sum of the products of the largest diameter and the perpendicular diameter for a tumor mass) on CT or MRI; FDG-PET may be positive (Deauville score or 4 or 5 with reduced lesional uptake compared with baseline); no new and/or PD; morphologic evidence of disease may be present in BM if present at diagnosis; however, there should be 50% reduction in percentage of lymphoma cells

Progressive Disease (PD): For those with > 25% increase in SPD on CT or MRI, Deauville score 4 or 5 on FDG-PET with increase in lesional uptake from baseline, or development of new morphologic evidence of disease in BM

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

10.2.7.2 Evaluation of Non-measured Lesions (CT-based response, PET/CT based response not applicable)[41]

Complete Response (CR): Absent non-measured lesions.

Partial response (PR): Absent/normal, regressed, lesions, but no increase.

Stable Disease (SD): No increase consistent with progression

Progressive Disease (PD): New or clear progression of preexisting non-measured lesions.

10.2.7.3 Evaluation of organ enlargement[41]

Complete Response (CR):	Regress to normal
Partial response (PR):	Spleen must have regressed by > 50% in length beyond normal
Stable Disease (SD):	No increase consistent with progression
Progressive Disease (PD):	In the setting of splenomegaly, the splenic length must increase by 50% of the extent of its prior increase beyond baseline. If no prior splenomegaly, must increase by at least 2 cm from baseline. New or recurrent splenomegaly

10.2.8 Duration of Response

10.2.8.1 Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

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

10.2.8.2 Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met.

10.2.9 Progression-Free Survival

PFS is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first.

10.2.10 Response Review

Response will be as per institutional evaluations.

11.0 ADVERSE EVENT REPORTING REQUIREMENTS

11.1 Purpose

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Certain adverse events must be reported in an expedited manner to allow for timelier monitoring of patient safety and care. The following sections provide information about expedited reporting.

11.2 Determination of Reporting Requirements

Reporting requirements may include the following considerations: 1) whether the patient has received an investigational or commercial agent; 2) the characteristics of the adverse event including the *grade* (severity), the *relationship to the study therapy* (attribution), and the *prior experience* (expectedness) of the adverse event; 3) the Phase (1, 2, or 3) of the trial; and 4) whether or not hospitalization or prolongation of hospitalization was associated with the event.

An investigational agent is a protocol drug administered under an Investigational New Drug Application (IND). In some instances, the investigational agent may be available commercially, but is actually being tested for indications not included in the approved package label.

Commercial agents are those agents not provided under an IND but obtained instead from a commercial source. The NCI, rather than a commercial distributor, may on some occasions distribute commercial agents for a trial.

When a study includes both investigational and commercial agents, the following rules apply.

- *Concurrent administration*: When an investigational agent is used in combination with a commercial agent, the combination is considered to be investigational and expedited reporting of adverse events would follow the guidelines for investigational agents.
- *Sequential administration*: When a study includes an investigational agent and a commercial agent on the same study arm, but the commercial agent is given for a period of time prior to starting the investigational agent, expedited reporting of adverse events which occur prior to starting the investigational agent would follow the guidelines for commercial agents. Once therapy with the investigational agent is initiated, all expedited reporting of adverse events follow the investigational agent reporting guidelines.

11.3 Expedited Reporting Requirements – Serious Adverse Events (SAEs)

To ensure compliance with these regulations/this guidance, NCI requires that AEs be submitted according to the timeframes in the AE reporting tables assigned to the protocol, using the CTEP Adverse Event Reporting System (CTEP-AERS).

Any AE that is serious qualifies for expedited reporting. An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. A Serious Adverse Event (SAE) is any adverse drug event (experience) occurring at any dose that results in ANY of the following outcomes:

1) Death.
2) A life-threatening adverse drug experience.
3) An adverse event resulting in inpatient hospitalization or prolongation of existing hospitalization (for ≥ 24 hours). This does not include hospitalizations that are part of routine medical practice.
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

11.4 Specific Examples for Expedited Reporting

11.4.1 SAEs Occurring More than 30 Days After Last Dose of Study Drug

Any Serious Adverse Event that occurs more than 30 days after the last administration of the investigational agent/intervention **and** has an attribution of a possible, probable, or definite relationship to the study therapy must be reported according to the CTEP-AERS reporting tables in this protocol.

11.4.2 Persistent or Significant Disabilities/Incapacities

Any AE that results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions (formerly referred to as disabilities), congenital anomalies or birth defects, must be reported via CTEP-AERS if it occurs at any time following treatment with an agent under a NCI, COG, or industry sponsor IND/IDE since these are considered to be serious AEs.

11.4.3 Death

Reportable Categories of Death

- Death attributable to a CTCAE term.
- Death Neonatal: A disorder characterized by cessation of life during the first 28 days of life.
- Sudden Death NOS: A sudden (defined as instant or within one hour of the onset of symptoms) or an unobserved cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
- Death NOS: A cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
- Death due to progressive disease should be reported as ***Grade 5*** *"Disease progression"* in the system organ class (SOC) "*General disorders and administration site conditions*". Evidence that the death was a manifestation of underlying disease (e.g., radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

Any death occurring ***within 30 days*** of the last dose, regardless of attribution to the investigational agent/intervention requires expedited reporting within 24 hours.

Any death occurring ***greater than 30 days*** after the last dose of the investigational agent/intervention requires expedited reporting within 24 hours **only if** it is possibly, probably, or definitely related to the investigational agent/intervention.

11.4.4 Secondary Malignancy

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

All secondary malignancies that occur following treatment need to be reported via CTEP-AERS. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy
- Myelodysplastic syndrome
- Treatment related secondary malignancy

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

11.4.5 Second Malignancy

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

11.4.6 Pregnancy, Pregnancy Loss, and Death Neonatal

NOTE: When submitting CTEP-AERS reports for "Pregnancy", "Pregnancy loss", or "Neonatal loss", the Pregnancy Information Form, available at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/PregnancyReportForm.pdf, needs to be completed and faxed along with any additional medical information to (301) 897-7404. The potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the "Description of Event" section of the CTEP-AERS report.

11.4.6.1 **Pregnancy**

Patients who become pregnant on study risk intrauterine exposure of the fetus to agents that may be teratogenic. For this reason, pregnancy needs to be reported in an expedited manner via CTEP-AERS as **Grade 3 "*Pregnancy, puerperium and perinatal conditions - Other (pregnancy)*"** under the ***Pregnancy, puerperium and perinatal conditions*** SOC.

Pregnancy needs to be followed **until the outcome is known**. If the baby is born with a birth defect or anomaly, then a second CTEP-AERS report is required.

11.4.6.2 Pregnancy Loss (**Fetal Death)**

Pregnancy loss is defined in CTCAE as "*Death in utero.*" Any Pregnancy loss should be reported expeditiously, as **Grade 4 "*Pregnancy loss*" under the "*Pregnancy, puerperium and perinatal***

***conditions*" SOC**. Do NOT report a pregnancy loss as a Grade 5 event since CTEP-AERS recognizes any Grade 5 event as a patient death.

11.4.6.3 **Death Neonatal**
Neonatal death, defined in CTCAE as *"Newborn death occurring during the first 28 days after birth*" should be reported expeditiously as **Grade 4 "*Death neonatal*" under the "*General disorders and administration*" SOC when the death is the result of a patient pregnancy or pregnancy in partners of men on study**. Do NOT report a neonatal death resulting from a patient pregnancy or pregnancy in partners of men on study as a Grade 5 event since CTEP-AERS recognizes any Grade 5 event as a patient death.

11.5 Reporting Requirements for Specialized AEs

11.5.1 Baseline AEs

Although a pertinent positive finding identified on baseline assessment is not an AE, when possible it is to be documented as "Course Zero" using CTCAE terminology and grade. An expedited AE report is not required if a patient is entered on a protocol with a pre-existing condition (e.g., elevated laboratory value, diarrhea). The baseline AE must be re-assessed throughout the study and reported if it fulfills expedited AE reporting guidelines.

a. If the pre-existing condition worsens in severity, the investigator must reassess the event to determine if an expedited report is required.
b. If the AE resolves and then recurs, the investigator must re-assess the event to determine if an expedited report is required.
c. No modification in grading is to be made to account for abnormalities existing at baseline.

11.5.2 Persistent AEs

A persistent AE is one that extends continuously, without resolution between treatment cycles/courses.
ROUTINE reporting: The AE must be reported only once unless the grade becomes more severe in a subsequent course. If the grade becomes more severe the AE must be reported again with the new grade.
EXPEDITED reporting: The AE must be reported only once unless the grade becomes more severe in the same or a subsequent course.

11.5.3 Recurrent AEs

A recurrent AE is one that occurs and resolves during a cycle/course of therapy and then reoccurs in a later cycle/course.
ROUTINE reporting: An AE that resolves and then recurs during a subsequent cycle/course must be reported by the routine procedures.
EXPEDITED reporting: An AE that resolves and then recurs during a subsequent cycle/course does not require CTEP-AERS reporting unless:

1) The grade increases OR
2) Hospitalization is associated with the recurring AE.

11.6 **Exceptions to Expedited Reporting**

An expedited report may not be required for a specific protocol where an AE is listed as expected. The exception or acceptable reporting procedures will be specified in the protocol. The protocol specific guidelines supersede the NCI Adverse Event Reporting Guidelines. These special situations are listed under the CTEP-AERS reporting Table A for this protocol.

11.7 **Reporting Requirements - Investigator Responsibility**

Clinical investigators in the treating institutions and ultimately the Study Chair have the primary responsibility for AE identification, documentation, grading, and assignment of attribution to the investigational agent/intervention. It is the responsibility of the treating physician to supply the medical documentation needed to support the expedited AE reports in a timely manner.

Note: All expedited AEs (reported via CTEP-AERS) must also be reported via routine reporting. Routine reporting is accomplished via the Adverse Event (AE) Case Report Form (CRF) within the study database.

11.8 **General Instructions for Expedited Reporting via CTEP-AERS**

The reporting methods described below are specific for clinical trials evaluating agents for which the IND is held by COG, an investigator, or a pharmaceutical company. It is important to note that these procedures differ slightly from those used for reporting AEs for clinical trials for which CTEP holds the IND.

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting.
All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website at:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

An expedited AE report must be submitted electronically via CTEP-AERS at:
https://eapps-ctep.nci.nih.gov/ctepaers

- Expedited AE reporting timelines are defined as:
  - **24-Hour; 5 Calendar Days -** The AE must initially be reported via CTEP-AERS within 24 hours of learning of the event, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
  - **7 Calendar Days -** A complete expedited report on the AE must be submitted within 7 calendar days of the investigator learning of the event.
- Any event that results in a persistent or significant incapacity/substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect, or is an IME, which based upon the medical judgment of the investigator may jeopardize the patient and require intervention to prevent a serious AE, must be reported via CTEP-AERS **if the event occurs following investigational agent administration.**
- Any death occurring within 30 days of the last dose, regardless of attribution to an agent/intervention requires expedited reporting **within 24 hours** via e-mail to the COG CTEP-AERS Coordinator and Study Chair.

- Any death occurring greater than 30 days of the last dose with an attribution of possible, probable, or definite to an agent/intervention requires expedited reporting **within 24 hours** via e-mail to the COG CTEP-AERS Coordinator and Study Chair.

CTEP-AERS Medical Reporting includes the following requirements as part of the report: 1) whether the patient has received at least one dose of an investigational agent on this study; 2) the characteristics of the adverse event including the *grade* (severity), the *relationship to the study therapy* (attribution), and the *prior experience* (expectedness) of the adverse event; 3) the Phase (1, 2, or 3) of the trial; and 4) whether or not hospitalization or prolongation of hospitalization was associated with the event.

Fax or email supporting documentation **for AEs related to investigational agents** to COG: Fax # (310) 640-9193; email: COGAERS@childrensoncologygroup.org; Attention: COG AERS Coordinator.

- **ALWAYS include the ticket number on all faxed documents.**
- **Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.**

11.9 Reporting Table for Late Phase 2 and Phase 3 Studies – Table A

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

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor (COG) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)
An adverse event is considered serious if it results in **ANY** of the following outcomes:
1) Death.
2) A life-threatening adverse event.
3) Any AE that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours. This does not include hospitalizations that are part of routine medical practice.
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6.)

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

<table>
<tr><th>Hospitalization</th><th>Grade 1 Timeframes</th><th>Grade 2 Timeframes</th><th>Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in Hospitalization ≥ 24 hrs</td><td colspan="3">7 Calendar Days</td><td rowspan="2">24-Hour Notification
5 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">Not Required</td><td>7 Calendar Days</td></tr>
</table>

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

Expedited AE reporting timelines are defined as:
"24-Hour; 5 Calendar Days" - The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour notification.
"7 Calendar Days" - A complete expedited report on the AE must be submitted within 7 calendar days of learning of the AE.

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

- All Grade 4, and Grade 5 AEs

Expedited 7 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

11.10 Protocol Specific Additional Instructions and Reporting Exceptions

- **Allograft rejection and/or failure requires expedited reporting.**
- **GvHD Grade 3 and higher (see Appendix V) requires expedited reporting.**

11.11 Reporting of Adverse Events for Commercial Agents – CTEP-AERS Abbreviated Pathway

The following are expedited reporting requirements for adverse events experienced by patients on study who have not received any doses of an investigational agent on this study. Commercial reporting requirements are provided in Table B.

COG requires the CTEP-AERS report to be submitted **within 7 calendar days** of learning of the event.

Table B
Reporting requirements for adverse events experienced by patients on study who have NOT received any doses of an investigational agent on this study.

CTEP-AERS Reporting Requirements for Adverse Events That Occur During Therapy with a Commercial Agent or Within 30 Days[1]

Attribution	**Grade 4**		**Grade 5**
	Unexpected	Expected	
Unrelated or Unlikely			CTEP-AERS
Possible, Probable, Definite	CTEP-AERS		CTEP-AERS

[1]This includes all deaths within 30 days of the last dose of treatment with a commercial agent, regardless of attribution. Any death that occurs more than 30 days after the last dose of treatment with a commercial agent that can be attributed (possibly, probably, or definitely) to the agent and is not due to cancer recurrence must be reported via CTEP-AERS.

11.12 Routine Adverse Event Reporting

Note: The guidelines below are for routine reporting of study specific adverse events on the COG case report forms and do not affect the requirements for CTEP-AERS reporting.

Routine reporting is accomplished via the Adverse Event (AE) Case Report Form (CRF) within the study database. For this study, routine reporting will include all CTEP-AERS reportable events and Grade 3 and higher Adverse Events, and all grades of the following: allograft failure, allograft rejection, cytokine release syndrome, and graft versus host disease (see Appendix V).

12.0 STUDY REPORTING AND MONITORING

The Case Report Forms and the submission schedule are posted on the COG web site with each protocol under "*Data Collection/Specimens*". A submission schedule is included.

12.1 CDUS

This study will be monitored by the Clinical Data Update System (CDUS) Version 3.0. Cumulative protocol- and patient-specific CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31 and October 31. CDUS reporting is not a responsibility of institutions participating in this trial.

12.2 Data and Safety Monitoring Committee

To protect the interests of patients and the scientific integrity for all clinical trial research by the Children's Oncology Group, the COG Data and Safety Monitoring Committee (DSMC) reviews reports of interim analyses of study toxicity and outcomes prepared by the study statistician, in conjunction with the study chair's report. The DSMC may recommend the study be modified or terminated based on these analyses.

Toxicity monitoring is also the responsibility of the study committee and any unexpected frequency of serious events on the trial are to be brought to the attention of the DSMC. The study statistician is responsible for the monitoring of the interim results and is expected to request DSMC review of any protocol issues s/he feels require special review. Any COG member may bring specific study concerns to the attention of the DSMC.

The DSMC approves major study modifications proposed by the study committee prior to implementation (e.g., termination, dropping an arm based on toxicity results or other trials reported, increasing target sample size, etc.). The DSMC determines whether and to whom outcome results may be released prior to the release of study results at the time specified in the protocol document.

13.0 PATHOLOGY GUIDELINES AND SPECIMEN REQUIREMENTS

13.1 Pathology Goals

- By retrospective review provide accurate diagnosis and classification of CD20 positive and EBV positive Post-Transplant Lymphoproliferative Disease (PTLD) in pediatric solid organ recipients included in this treatment protocol. The diagnosis to be based on both morphological and immunophenotypic criteria. As this is a retrospective review, results of the review will not be returned to the submitting site.

- Employ the World Health Organization Lymphoma Classification to facilitate concordance in diagnosis.

- Evaluate CD20+ and EBV+ PTLD included in this protocol for immunophenotypic and pathologic features that may impact prognosis.

13.2 Requirements for Handling Tissue or Cytology Specimens at Primary Institutions

Tissue should, whenever possible, be obtained fresh and delivered immediately to the Pathology laboratory for optimal handling and distribution (fixation, snap freezing, cytogenetics, etc.)

Representative tissue sections should be submitted for fixation including at least one block with 10% buffered formalin.

13.3 Immunophenotyping Recommendations for Primary Institutions

For initial determination of cell lineage the methodology and criteria for immunophenotypic analysis defined by the submitting institution will be accepted. Recognized methods include paraffin section, immunohistochemistry, flow cytometry and cytospin immunocytochemistry.

13.3.1 Required Antibodies/In-Situ Hybridization:

- CD20
- EBER (preferred) and/or LMP-1

13.3.2 Recommended antibodies

- At least one additional anti-B antibody (CD79A, PAX-5)
- At least two anti-T antibodies (CD3 and one other T-cell specific antibody)

13.4 Morphology

The following are recognized morphological variants of PTLD that should be diagnosed according to the criteria established by the WHO Classification.[9]

- Mononucleosis-like
- Plasma cell hyperplasia
- Polymorphic
- Monomorphic
- Classical Hodgkin-like

13.5 Study Pathologist

For any questions regarding the pathology protocol or assistance with immunophenotyping studies, contact the pathologist listed below. Difficult cases may also be reviewed in consultation prior to enrollment with the pathologists listed below.

14.0 SPECIMENS TO SUBMIT FOR CENTRAL PATHOLOGY REVIEW

14.1 List of Specimen Types

Materials to be submitted for retrospective pathology review are not required but strongly encouraged. If possible, please submit the following materials to the COG Biopathology Center (BPC):

1. Representative sample, (paraffin embedded material, 1 or 2 blocks) from tumor biopsy at original diagnosis, time of relapse (if applicable) and time the patient was confirmed to be refractory (if applicable).
    a. If blocks are unavailable submit 30 unstained slides from one representative block and 2 H&E slides from each available block. For surgical biopsy specimens 10% buffered formalin is the preferred fixative. Please submit unbaked slides that are air dried at room temperature for the unstained slides. Sections should be cut on silane-coated slides (i.e. Fisher Superfrost Plus).
    b. For cytologic specimens, at least 10 unstained cytology slides or (preferably) 20 slides from a cell block preparation, prepared as outlined for surgical specimens above, should be submitted.

14.2 Pathology Reports and Transmittal Form

All corresponding pathology reports and ancillary testing (i.e. flow cytometry, cytogenetics) for each case **must** be submitted. These are required even if no blocks or slides were sent. Please include reports from original diagnosis, time of relapse (if applicable) and time the patient was confirmed to be refractory (if applicable). This should include:

1. Final pathology reports of all diagnostic biopsies, bone marrow specimens, and cerebrospinal fluid specimens including all immunophenotyping reports of diagnostic biopsy, bone marrow specimens and cerebrospinal fluid specimens (if available);
2. Results of any genotypic studies (i.e. gene rearrangement or fluorescent in-situ hybridization studies); and
3. Results of any cytogenetic (karyotypic) analysis.
4. Pathology Data Collection Forms (Institutional Pathology Form).
   A separate pathology data collection form (Institutional Pathology Form) must be completed and submitted along with the above materials. Also, indicate the primary institution pathology diagnosis utilizing the WHO Classification criteria[9] on the data collection form.
5. COG Pathology Transmittal Form along with the Pathology Data Collection Form (Institutional Pathology Form).

14.3 Submission of Pathology Review Materials

Label all review materials with the patient's COG patient ID number and the surgical pathology identification number and block number from the corresponding pathology report. Send a completed COG Pathology Transmittal Form with the pathology review materials by U.S. mail or using your institution's courier account. All material submitted for central pathology review should be sent to:

Biopathology Center Nationwide Children's Hospital
700 Children's Drive, WA 1340
Columbus, OH 43205
Phone: (614) 722-2865
Fax: (614) 722-2897

Email: BPCParaffinTeam@nationwidechildrens.org

15.0 SPECIAL STUDIES SPECIMEN REQUIREMENTS

15.1 Table of Specimens

Study	Time points	Collection Details	Additional Details	Mailing Destination
15.1.1 **EBV PCR** Required from all patients	• **RTX1**: Days 1 & 21 • **RTX2**: Days 1 & 21 • **LMP-TC1**: Days 0, 14, & 41 • **LMP-TC2**: Days 0, 14, & 41 • **Follow-up**: Months 1, 2, 3, 6, 9 & 12	Draw 5 mL of whole blood in a EDTA (purple top) tube.	Store at room temperature. Ship on the day of collection. **Do not freeze samples**.	Allen Lab at Baylor College of Medicine (BCM) Section 15.3.4
15.1.2 **General Immune Reconstitution** (Optional patient consent required)	• **RTX2**: Days 1, 8, 15, & 21 • After completing **RTX2*:** Weeks 6, 8, Months 3, 6, 9 & 12 • **LMP-TC1**: Days 0, 7, 14, 28 & 41 • After completing **LMP-TC1**[#]: Week 8, Months 3, 6, 9 & 12	Draw 6-12 mL of whole blood in a sodium heparin (green top) tube.	Store at room temperature. Ship on the day of collection. **Do not freeze samples**.	Allen Lab at BCM Section 15.3.4
15.1.3 **Persistence of LMP-specific T cells; Immunity to EBV** (Optional patient consent required)	• **RTX2**: Days 1, 8, 15 & 21 • After completing **RTX2*:** Weeks 6 & 8 • **LMP-TC1**: Days 0, 7, 14, 28 & 41 • After completing **LMP-TC1**[#]: Week 8	Draw 6-12 mL of whole blood in a sodium heparin (green top) tube.	Store at room temperature. Ship on the day of collection. **Do not freeze samples**.	Allen Lab at BCM Section 15.3.4
15.1.4 **Cytokine Release Syndrome** (Optional patient consent required)	In case a late reaction necessitates clinical labs to assess for cytokine release syndrome	Draw 6-12 mL of whole blood in a sodium heparin (green top) tube.	Store at room temperature. Ship on the day of collection. **Do not freeze samples**.	Allen Lab at BCM Section 15.3.4
15.1.5 **Allograft Rejection or Failure** (Optional patient consent required)	If allograft rejection or failure occurs during LMP-TC1 or LMP-TC2. Please draw before initiation of any immunosuppression.	Draw 12-20 mL of whole blood in a sodium heparin (green top) tube.	Store at room temperature. Ship on the day of collection. **Do not freeze samples**.	Bollard Lab at CNMC Section 15.3.5

***** Time point calculated from Day 1 of RTX2.

[#] Time point calculated from Day 0 of LMP-TC1 regardless of treatment on Course LMP-TC2.

15.2 Blood Sample Collection

15.2.1 Whenever a specimen collection time falls on a treatment infusion day, blood must be drawn prior to initiation of the infusion.

15.2.2 The indicated time points in the table above represent the ideal schedule. Flexibility is expected in order to coordinate with times of blood draw for regular clinical care:

- After Course LMP-TC1 or RTX2 or during follow-up time points at Week 6, Week 8 and Months 2 & 3: variations of up to 2 days before/after scheduled dates are acceptable.
- For the later time points Months 6, 9, 12: variations of up to 4 weeks are acceptable.

15.2.3 Missed Time Points: If biology specimens are not obtained at any requested time point, please send specimens at the next requested time point or at the next clinic visit, whichever is sooner. Please note that EBV PCR is a required specimen on this study.

15.3 Blood Specimen Shipping

A COG Generic Specimen Transmittal Form should accompany each shipment.

15.3.1 Packing of Peripheral Blood Samples

Blood should be packaged for shipping according to institutional protocol for the packaging and shipping of blood products.

15.3.2 IATA standards

When shipping blood, please be aware that your institution must comply with IATA standards (www.iata.org).

15.3.3 Shipping Conditions

All samples should be shipped at ambient temperature in a thick Styrofoam container to provide temperature stability. Ship overnight Monday to Thursday only for Tuesday-Friday arrival. Notify the Lab Contact Person prior to shipment.

Samples will not be accepted on Saturdays.

Blood should be shipped to the BCM and CNMC Labs at the addresses indicated below using the COG FedEx account https://members.childrensoncologygroup.org/_files/reference/FEDEXmemo.pdf.

15.3.4 Shipping Address at BCM

[redacted]

15.3.5 Shipping Address at CETI at CNMC

[redacted]

15.4 **Rationale and Methods for Biology Aims**

In brief, the rationale of the biology studies is that biomarkers reflecting immune response may predict efficacy and toxicity of therapy. Methods will depend on available samples. Assays to be performed may include:

15.4.1 Evaluation of general immune reconstitution via immunophenotyping and cytokine analysis.

15.4.2 Investigation of persistence of LMP-specific T cells and immunity to EBV via HLA-tetramer assays and/or Enzyme-linked Immunospot (ELISPOT) assays

15.4.3 Evaluation of EBV viral load pre and post T-cell infusions using serial PCR-based assays to monitor EBV DNA levels in the peripheral blood.

See Appendix IV for a more detailed overview of the rationale, hypotheses, and methods for the Biology Aims.

15.5 **Specimen Disposition**

Specimens will be received at BCM or CNMC, aliquoted and either assayed immediately or frozen for subsequent correlative study procedures. After the analyses are completed, any remaining sample will be destroyed.

16.0 IMAGING STUDIES REQUIRED AND GUIDELINES FOR OBTAINING

Timing of protocol therapy administration, response assessment studies, and surgical interventions are based on schedules derived from the experimental design or on established standards of care. Minor unavoidable departures (up to 72 hours) from protocol directed therapy and/or disease evaluations (and up to 1 week for surgery) for valid clinical, patient and family logistical, or facility, procedure and/or anesthesia scheduling issues are acceptable (except where explicitly prohibited within the protocol).

16.1 Computed Tomography (CT) with Contrast

Most, if not all, COG institutions will be using multi-detector helical CT scanners. This is preferred in order to decrease scanning time compared to conventional CT, allow image acquisition at the time of peak contrast enhancement, reduce/eliminate the need for sedation, and reduce image degradation from motion artifact. The volumetric acquisition of helical/spiral CT and the reconstruction of overlapping images increases the conspicuity of small lesions and facilitates multi-planar reconstruction for better depiction of certain lesions. Sagittal and coronal reconstructed images, as well as images reconstructed using a lung algorithm should be submitted where feasible, along with the axial imaging data. CT imaging should be performed with intravenous and oral contrast using age and weight-based adjustments to kVp and mA, in accordance with institutional practice and ALARA/Image Gently guidelines. Timing of protocol therapy administration, response assessment studies, and surgical interventions are based on schedules derived from the experimental design or on established standards of care. Minor unavoidable departures (up to 72 hours) from protocol directed therapy and/or disease evaluations (and up to 1 week for surgery) for valid clinical, patient and family logistical, or facility, procedure and/or anesthesia scheduling issues are acceptable (except where explicitly prohibited within the protocol).

MRI may be used as an alternative modality for assessment of non-pulmonary disease sites (e.g. abdominal/pelvic disease), provided the institution is able to acquire images using phased array surface coils, cardiac gating and respiratory triggering, in order to minimize artifacts from cardiac motion, diaphragmatic motion and bowel peristalsis. Pulse sequences should include at a minimum axial and coronal fat-saturated FRFSE-T2, coronal T1 and axial and coronal post-gadolinium fat-saturated T1 weighted imaging. If MRI is used for imaging of the thorax, abdomen and/or pelvis, an unenhanced CT of the chest should still be obtained to evaluate the lungs.

16.2 CT during PET/CT

Nearly all PET scanners in use today are integrated PET/CT scanners. However, low dose CT scans performed on integrated PET/CT scanners for the purpose of attenuation correction are of non-diagnostic quality, are usually performed without intravenous contrast, and will not be acceptable for staging or response assessment. As noted above, staging CT scans should include intravenous and oral contrast. In some instances – particularly for staging – a diagnostic quality CT will have been performed prior to the PET/CT. In these cases an additional low-dose CT will still be required for attenuation correction of the PET images. Provided that the diagnostic quality CT scan has been performed within 14 days of the PET/CT, a repeat diagnostic CT examination is not necessary at the time of PET/CT. For post-therapy follow-up scans limited to the neck and/or thorax the use of IV contrast alone is sufficient, provided the scanning parameters are optimized to achieve diagnostic quality images. Some institutions

perform the low dose attenuation correction CT with intravenous contrast. Please refer to Section 10.2.6.3 for the requirements.

16.3 [^{18}F] Fluorodeoxyglucose (FDG) PET

The use of PET scans is optional but highly recommended. If there is positive disease by PET scan at diagnosis, PET scans have to be performed at repeat evaluation time points until the patient has achieved a CR.

17.0 RADIATION THERAPY GUIDELINES

No radiation therapy is planned for this study.

APPENDIX I: CTEP AND CTSU REGISTRATION PROCEDURES

CTEP INVESTIGATOR REGISTRATION PROCEDURES

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account (https://ctepcore.nci.nih.gov/iam). In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) (i.e., clinical site staff requiring write access to OPEN, RAVE, or TRIAD or acting as a primary site contact) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) (https://ctepcore.nci.nih.gov/rcr). Documentation requirements per registration type are outlined in the table below.

Documentation Required	IVR	NPIVR	AP	A
FDA Form 1572	✔	✔		
Financial Disclosure Form	✔	✔	✔	
NCI Biosketch (education, training, employment, license, and certification)	✔	✔	✔	
HSP/GCP training	✔	✔	✔	
Agent Shipment Form (if applicable)	✔			
CV (optional)	✔	✔	✔	

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

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

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

CTSU REGISTRATION PROCEDURES

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

Downloading Site Registration Documents:

Site registration forms may be downloaded from the ANHL1522 protocol page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU RSS.

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Protocols tab in the upper left of your screen
- Either enter the protocol # in the search field at the top of the protocol tree, or
- Click on the By Lead Organization folder to expand
- Click on the COG link to expand, then select trial protocol #ANHL1522
  Click on LPO Documents, select the Site Registration documents link, and download and complete the forms provided.

Requirements For ANHL1522 **Site Registration:**

- IRB approval (For sites not participating via the NCI CIRB; local IRB documentation, an IRB-signed CTSU IRB Certification Form, Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form, or combination is accepted)

Submitting Regulatory Documents:

Submit required forms and documents to the CTSU Regulatory Office, where they will be entered and tracked in the CTSU RSS.

Regulatory Submission Portal: www.ctsu.org (members' area) → Regulatory Tab →Regulatory Submission

When applicable, original documents should be mailed to:
CTSU Regulatory Office
1818 Market Street, Suite 3000
Philadelphia, PA 19103

Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support.

Checking Your Site's Registration Status:

You can verify your site registration status on the members' section of the CTSU website. Note: Sites will not receive formal notification of regulatory approval from the CTSU Regulatory Office.

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Regulatory tab at the top of your screen
- Click on the Site Registration tab
- Enter your 5-character CTEP Institution Code and click on Go

Note: The status given only reflects compliance with IRB documentation and institutional compliance with protocol-specific requirements as outlined by the Lead Network. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

Data Submission / Data Reporting

Data collection for this study will be done exclusively through the Medidata Rave clinical data management system. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in Regulatory Support System (RSS). To access Rave via iMedidata, the site user must have an active CTEP-IAM account (check at https://ctepcore.nci.nih.gov/iam) and the appropriate Rave role (Rave CRA, Read-Only, CRA (Lab Admin, SLA or Site Investigator) on either the LPO or participating organization roster at the enrolling site. To the hold Rave CRA role or CRA Lab Admin role, the user must hold a minimum of an AP registration type. To hold the Rave Site Investigator role, the individual must be registered as an NPIVR or IVR. Associates can hold read-only roles in Rave. If the study has a DTL, individuals requiring write access to Rave must also be assigned the appropriate Rave tasks on the DTL.

Upon initial site registration approval for the study in RSS, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site users must log into the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM user name and password, and click on the "accept" link in the upper right-corner of the iMedidata page. Please note, site users will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings), and can be accessed by clicking on the link in the upper right pane of the iMedidata screen.

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

APPENDIX II: RITUXIMAB OR BIOSIMILAR INFUSION GUIDELINES

Special precaution: Due to the risk of hypotension, hold antihypertensive medications 12 hours prior to infusion.

Dose = 375 mg/m^2

1. Dilute in NS or D5W to a final concentration of 1-4 mg/mL. Consider 1 mg/mL concentration for ease of administration and rate titration.
2. Administer intravenously through a dedicated line (should not be mixed or diluted with other drugs)
3. Premedication recommended 30-60 minutes prior to each dose with:
   Acetaminophen 10-15 mg/kg PO (max 650 mg)
   Diphenhydramine 1 mg/kg IV or PO (max 50 mg)

FIRST INFUSION:

1. **Initial rate**:
   - In patients **< 18 years** of age:
     - 0.5 mg/kg/hr (maximum of 50 mg/hr) for the 1st hour, or
   - In patients ≥ **18 years** of age:
     - 50 mg/hr for the 1st hour.

2. **If no hypersensitivity or infusion-related events**:
   - In patients **< 18 years** of age:
     - Increase infusion rate by 0.5 mg/kg/hr (maximum 50 mg/hr increase) every 30 minutes, to a maximum rate of 400 mg/hr as tolerated, or
   - In patients ≥ **18 years** of age:
     - Increase infusion rate by 50 mg/hr every 30 minutes to a maximum rate of 400 mg/hr as tolerated.

3. **If a hypersensitivity or infusion related event develops for patients at any age**:
   - The infusion should be slowed or interrupted
   - The infusion can continue at one half the previous rate upon improvement of patient symptoms

SUBSEQUENT INFUSIONS (if the patient tolerated the first infusion well):

1. **Initial rate**:
   - In patients **< 18 years** of age:
     - 1 mg/kg/hr (maximum 100 mg/hr) for the 1st hour, or
   - In patients **≥ 18 years** of age:
     - 100 mg/hr for the 1st hour

2. **If no hypersensitivity or infusion-related events**:
   - In patients **< 18 years** of age:
     - Increase infusion rate by 1 mg/kg/hr (maximum 100 mg/hr) every 30 minutes, to a maximum rate of 400 mg/hr as tolerated.
   - In patients ≥ **18 years** of age:
     - Increase infusion rate by 100 mg/hr every 30 minutes, to a maximum rate of 400 mg/hr as tolerated.

3. **If a hypersensitivity or infusion related event develops at any age**:
    - The infusion should be slowed or interrupted
    - The infusion can continue at one half the previous rate upon improvement of patient's symptoms

If the patient did not tolerate the first infusion well subsequent infusions should be given following the guidelines under First Infusion.

Nursing Implications:

1. Monitor blood pressure, pulse, respiration and temperature every 15 minutes for the first hour or until the patient is stable, then hourly until the infusion is complete.
2. Have epinephrine, diphenhydramine and corticosteroids available along with resuscitation equipment for the emergency management of anaphylactic reactions.
3. If infusion related events occur, slow the infusion or stop the infusion until resolution, treating the patient if necessary. If it is determined that the patient can be safely rechallenged, begin the infusion at 50% of the rate at which the infusion was running when stopped.
4. Verify that the patient has not taken antihypertensive medications within 12 hours of beginning the Rituximab infusion. Hypotension may occur during the infusion.
5. A high number of circulating cancer cells (> 25,000/mm^3) in patients may indicate a higher risk for tumor lysis syndrome. These patients should receive allopurinol and intravenous hydration and should be monitored.
6. Patients that experience severe infusional symptoms may need to be hospitalized for observation. Patients should be counseled to be seen in the emergency room if infusion related symptoms occur again after the infusion is complete (i.e. at home at a later time).
7. Monitor patients during and for a few weeks after receiving Rituximab for the development of mucositis with a sore throat or mouth ulcers followed by a diffuse skin rash which can worsen rapidly and result in total body skin sloughing and can become life threatening.
8. See Section 5.0 for criteria for discontinuation of Rituximab.

APPENDIX III: GUIDELINES FOR LMP-SPECIFIC T CELL PRODUCT

I. Selection of LMP-specific T Cell Product

The most appropriate LMP-specific T-cell product will be selected based on degree of HLA matching and number of shared alleles with LMP activity.

II. Product Storage

A. The LMP-specific T-cell product will be stored in the vapor phase of liquid nitrogen in a continuously monitored cell bank at the Program for Cell Enhancement and Technologies for Immunotherapy (CETI) at Children's National Medical Center. At the time of shipment, the product will be removed from inventory following Standard Operating Procedures for product release. The cryogenic vial(s) will be placed in a qualified charged liquid nitrogen dry shipper equipped with a continuous temperature monitor. The shipper will be labeled to comply with FACT and IATA standards and transported by a qualified courier using Priority Overnight service.

B. The receiving institution will be notified of the shipment and the tracking number provided. Upon receipt, the integrity of the product and the temperature of the shipper will be documented. The temperature recorder will be stopped, and the product transferred to liquid nitrogen storage at the site's Stem Cell Transplantation facility or thawed upon receipt.

C. The shipper will be returned to CETI at CNMC by a qualified courier, and the data from the temperature logger downloaded and printed. The shipping information will be retained at CETI and a copy sent to the receiving facility.

III. Product Labeling

These are Third Party donor derived HLA matched LMP-specific T cells and are labeled with the coded name (P#), product-specific donor identification number (DIN number), product type (LMP-specific T cells), date of manufacture and cell dose. The dose of cells in this study is $2 \times 10^7/m^2$.

IV. Product Administration

The product will be thawed and infused in accordance with the Standard Operating Procedure that follows. Prior to administration, premedication is recommended with diphenhydramine 1 mg/kg (max 50 mg) PO or IV and acetaminophen 10-15 mg/kg (max 650 mg) PO 30-60 minutes prior to infusion. LMP-specific T cells (2×10^7cells/m^2) will be thawed according to the instructions below and administered IV 30-60 minutes after diphenhydramine and acetaminophen (as applicable). All institutions participating in this study are FACT accredited.

A. Thawing of LMP-specific T Cell Products

1. LMP-specific T cells are supplied in vial(s) that are transported from liquid nitrogen storage at GMP CETI at CNMC to the site of infusion in liquid nitrogen in a suitable container.
2. When the transplant physician/designee is ready, remove the component vial(s) from the liquid nitrogen with a pair of hemostats. Two physicians or a physician and nurse must check the patient's name and medical record number on the vial(s) against the patient's name and medical record number on the receipt/storage worksheet supplied with the shipment. Any discrepancy MUST be investigated prior to thawing the product.
3. Place the cryopreserved LMP-specific T-cell vial(s) in a sterile overwrap bag and seal.
4. Submerse in a 37° C water bath filled with sterile water.

5. When the product has thawed to a slushy consistency, remove the vial(s) from water bath, spray with 70% ethanol and dry with a towel.
6. The product is to be transferred to a sterile syringe for intravenous administration. The physician should only draw up the appropriate volume into the syringe as designated on the prescription. The syringe should be labeled with the recipient's name, medical record number, date of thaw and product name (LMP-specific T cells).
7. The thawed vial(s) should be saved and a sample removed for viability and bacterial (aerobic and anaerobic) and fungal culture according to the institution's standard procedures.

B. Infusion of LMP-specific T Cells

1. Nursing staff will ensure that patient has IV access and that the line contains a stopcock for LMP-specific T-cell infusion. Normal saline should be running through the IV line to be accessed.
2. Nursing staff will prepare for emergency procedure by ensuring that oxygen and suction equipment are available in the patient room, according to institution's SOPs, which include availability of emergency drugs and equipment (i.e. epinephrine, diphenhydramine, hydrocortisone or methylprednisolone). In addition, baseline vital signs are documented.
3. The LMP-specific T-cell product will be infused as soon as possible after thawing
4. Two licensed staff will identify the patient by verifying the information on the patient armband and the component with a check of the identification bracelet on the recipient for correct name and hospital number, as per institution's SOP, against the product.
5. The LMP-specific T-cell product will be given through peripheral or central intravenous line over 1 minute and flushed with sterile saline.

V. Management of Adverse Reactions to LMP-specific T Cell Infusions

LMP-specific T cells infusions are typically well tolerated but adverse reactions may occur early (within 24 hours of infusion) or late (greater than 24 hours after infusion). Early reactions are usually related to the cryopreserved components.

A. Monitoring Post LMP-specific T Cell Infusion

Medical staff will assess for any adverse effects for 1 hour post-infusion. Vital signs should be monitored immediately at end of infusion then at 30 and 60 minutes. Patients should remain on continuous pulse oximetry for at least 30 minutes after infusion.

1. Common, mild complications from LMP-specific T-cell infusion include:
   - Mild increase in blood pressure not requiring intervention
   - Mild headache
   - Mild flushing
   - Slight slowing of the heart rate
   - Bad taste in mouth

2. Severe early reactions from LMP-specific T-cell infusion are rare but may include:
   - Acute pulmonary edema and dyspnea
   - Persistent nausea and vomiting
   - Sustained or significant increase in blood pressure
   - Fever
   - Anaphylactic shock

- Bradycardia or cardiac arrest

B. Management of Early Reactions

Most common, mild early reactions do not require intervention.

1. Management of anaphylaxis: Emergency medications should be ordered in advance and available at the patient's bedside at the time of infusion. Hydrocortisone (or other steroids) should not be administered without approval of physician administering LMP-specific T cells.
   - Hydrocortisone 5-10 mg/kg IV (maximum 500 mg) or methylprednisolone 1-2 mg/kg IV (maximum 125 mg)
   - Epinephrine 0.01 mg/kg IM (preferred) or SubQ (maximum 0.5 mg; 0.01 mL/kg of 1 mg/mL solution, maximum of 0.5 mL)
2. In the event of a severe reaction, the patient should be immediately transferred to emergency room or intensive care unit for intensive monitoring and intervention, which usually includes blood pressure support, steroids, and management of anaphylaxis.

C. Monitoring and Management of Late Reactions

Late reactions to LMP-specific T cells infusion are rare. The following details regarding signs/symptoms and management, follow (Source: CETI SOP SCTCP-27 Management of Adverse Reactions to T-Lymphocyte Infusions, Version 1.2, Effective Date: 2016-03-21)

1. Late reactions to T-cell infusion may be related to a T-cell engraftment syndrome or cytokine release syndrome (CRS), tumor lysis syndrome, and rarely to contamination of the product.

2. Symptoms and signs of late complications from infusion of T-cell products may include:

Systemic	fever malaise, fatigue myalgias and arthralgias skin rash mimicking acute GvHD general feeling of unwellness disseminated intravascular coagulation (DIC) +/- bleeding macrophage activation syndrome/hemophagocytotic lymphohistiocytosis (HLH) anorexia, nausea, vomiting, diarrhea
Cardiorespiratory	tachycardia blood pressure changes (either hyper- or hypotension) acute pulmonary edema, dyspnea, hypoxia pulmonary infiltrates capillary leak syndrome cardiac dysfunction stress cardiomyopathy (Takotsubo cardiomyopathy) adult respiratory distress syndrome (ARDS)

Hepatic and Renal	weight gain renal impairment azotemia hyperuricemia hepatic impairment – transaminitis, hyperbilirubinemia
Neurological	headache mental status changes confusion delirium hallucinations altered gait seizures encephalopathy mild encephalopathy with reversible splenial lesion syndrome (MERS)

3. Management of Late Reactions

(1) The development of a severe late reaction necessitates immediate notification of the PI and ANHL1522 Study Chair AND (if an outpatient) transfer to the hospital for an urgent medical assessment. It is important to evaluate the patient and initiate therapy as quickly as possible since rapid deterioration is possible.

(2) Biomarkers: Circulating cytokine levels can serve as biomarkers to diagnose and potentially quantify syndrome severity.
(a) IL-6 signaling is major component of severe cytokine release syndrome
(b) If possible, cytokine levels should be sent to Viracor prior to starting any anticytokine directed therapy. See Section 15 for corresponding optional research specimen submission.
(c) CRP serves as a reliable surrogate for IL-6 bioactivity and levels should be sent pre and post therapy to monitor response
(d) Ferritin may also be used in conjunction with CRP monitoring

(3) The immediate assessment and treatment may also include:
(a) Intensive monitoring (BP, cardiovascular monitoring, pulse oximetry or ABG)
(b) CXR or CT of chest
(c) Steroids – single dose. See #(4) below
(d) Microbiological studies (especially blood cultures and virus studies) and initiation of broad-spectrum antibiotics +/- antivirals should be considered.
(e) Blood pressure/Cardiovascular support – early institution of inotropic medications. Limit fluid resuscitation to the minimum volume needed to support blood pressure, no more than 20 mL/kg, (up to 1,000 mL), if possible.
(f) Fluid management/Renal support – Aggressive diuresis. Institute early involvement of the renal service for fluid management especially if evidence of capillary leak syndrome. Consider infusion of 25% albumin if serum albumin is < 3 g/dL.
(g) Respiratory support – supplemental oxygen therapy should be initiated for all hypoxemic patients. Patients also may require intubation and mechanical ventilation.
(h) Management of tumor lysis syndrome if there is laboratory evidence it is occurring.

(4) Treatment of the cytokine release syndrome or other T-cell associated adverse reactions must be discussed with the PI and ANHL1522 Study Chair. If the situation is emergent, the first dose of steroids can be given prior to consultation with the PI.

In general, the cytokine release syndrome is managed similarly to engraftment syndrome EXCEPT:

- As the patient received an investigational T-cell agent, steroids may not be considered first line therapy and anti-IL-6 directed therapy MAY be given without first starting steroids.
- When managing CRS, anti-IL-6 directed therapy should be initiated before anti-TNFa directed therapy.
- Caution is required when using tocilizumab in the setting of hepatic impairment.

(5) If treatment with a biological agent is necessary, the order of priority will usually be:

- Tocilizumab
- Infliximab (anti-TNFa)
- Etanercept (soluble TNFa receptor inhibitor)

Drug	Dosing	Duration
Tocilizumab	<30 kg: 12 mg/kg IV ≥30 kg: 8 mg/kg (maximum 800 mg) IV	One dose, with repeat dosing if no improvement observed within 24-48 hours.
Infliximab	10 mg/kg IV	One dose, may give second 3-4 days later
Etanercept	0.4 mg/kg (maximum 25 mg) SubQ	One dose, may give second 3-4 days later

APPENDIX IV: CORRELATIVE BIOLOGY STUDIES

Immune Reconstitution, Persistence of LMP-specific T Cells, and EBV Viremia

1V.1 Background:

The goal of the correlative biology studies is to test the hypothesis that LMP-specific T cells aid in the immune reconstitution of patients with EBV positive PTLD. In addition, we are testing the hypothesis that third party LMP-specific T cells may aid in autologous immune reconstitution that persists once the third party LMP-specific T cells have been cleared and that EBV viremia as measured by EBV PCR is inversely correlated with absence of EBV-specific T cells and can predict risk for relapse as shown in our previous publications using autologous EBV-specific T cells.[26,27] Finally, these studies will determine the ability of plasma cytokine profiles to predict and measure response to therapy and toxicity in patients treated with EBV-specific T cells.

If autologous immune reconstitution in response to third party LMP-specific T cells occurs, it would be expected to reduce the risk of future EBV-related lymphoproliferation without the need for long-term persistence of the third party LMP-specific T cells or repeated LMP-specific T cells administrations. Third party LMP-specific T cells have the main advantage to be readily available without delay when needed because they can be produced from healthy donors to cover the most prevalent HLA phenotypes and be stored in a cell bank. If they also aid in autologous immune reconstitution without the need of persistence, there would be a rationale of further clinical development of third party cellular therapy because it could be widely and easily available without the need and delays of "custom-made" cellular therapies and without the unknown risks of persistence of modified cells in the host.

IV.2 [redacted]

3. [redacted]

A. General Immune reconstitution

Hypothesis and Rationale: Third Party LMP-specific T cells in combination with rituximab will be superior in aiding the immune reconstitution of the recipients compared to rituximab alone. The rationale behind this correlative study is that EBV positive PTLD is caused by a defective immune system and LMP-specific T cells lead to EBV specific immune reconstitution. Monitoring occurrence and persistence of this immune reconstitution may be able to predict response and/or risk of recurrence of PTLD. Studies to evaluate general immune reconstitution will include:

I. Immunophenotyping

Sample Requirement: 3-6 ml whole blood in sodium heparin (green top)

Method: We will first characterize the phenotype of the T cells (gating on EBV tetramer+ (tet) T cells if informative tetramers are available) in the PBMCs. General T-cell markers including memory markers may be used when sufficient PBMC are available - for example: CD4, CD8, CD45RA, CD45RO, CD62L, CD27, CD28, and chemokine receptor expression (e.g. CCR7, CCR4 and CXCR3 and CLA) by flow cytometry.

II. Cytokine Analysis
Sample Requirement: 3-6 ml whole blood in sodium heparin (green top)
Method: Cytokine release by the T cells will be evaluated luminex assay and/or intracellular cytokine assay (e.g. for tet+ IFNg/IL-2 double secreting CM T cells) and/or Cytokine Bead Array when sufficient PBMC are available and informative tetramers are available.[42]

B. Persistence of LMP-specific T Cells and Immunity to EBV

Hypothesis and Rationale: EBV lymphoproliferation is controlled by the presence of EBV-specific T cells. Persistent absence of EBV viremia as measured by EBV PCR in the blood is able to predict the presence of EBV-specific T cells and the risk of recurrence. The rationale behind this correlative study is that it is currently unknown what the adequate post-therapy monitoring is for this patient population that receives ongoing immune suppression. Serial CT and/or PET scans carry significant radiation exposure. Developing reliable biomarkers would be of significant clinical importance to avoid unnecessary radiation exposure and/or invasive procedures. Studies planned for evaluation of persistence of LMP-specific T Cells and Immunity to EBV include:

I. Tetramer Staining
Sample Requirement: 3-6 ml whole blood in sodium heparin (green top)
Method: T-cell frequencies may be measured in HLA-tetramer assays when informative tetramers are available. These functional analyses MUST be performed on fresh samples to ensure consistency of the analysis both intra- and inter- patient.[43]

II. Enzyme-Linked Immunospot (ELISPOT) Assay
Sample Requirement: 3-6ml whole blood in sodium heparin (green top)
Method: ELISPOT assays using third party donor EBV-LCL to stimulate EBV-specific T cells in patient PBMC may be utilized to evaluate EBV specific T-cell frequencies. As a control, CMV-derived peptides can be used to measure CMV-specific responses.[44] A 0.5 log or greater increment in the frequency of EBV specific T cells from one time point to the next will be taken as indicative of a significant expansion of EBV specific T cells in vivo.

C. Detection of EBV DNA
Sample Requirement: 5 ml whole blood in EDTA (purple top)
Method: Serial blood samples will be used to follow EBV viremia using PCR based assays and analyzed with respect to clinical outcomes. Due to the wide variability of results from EBV quantification methods using different assays and different blood fractions (e.g. plasma versus white blood cells), these studies will be performed with a CLIA-certified assay at Baylor College of Medicine. This surveillance will enable establishment of endpoints for correlating EBV specific T-cell immune reconstitution with effects on PTLD/EBV viral load.

IV.3 Justification for collection of fresh samples:
All correlative biology studies will be performed on peripheral blood samples. The above described studies require fresh blood samples shipped overnight because they are largely functional studies that require processing prior to freezing and storing. Samples will be batched and testing will be performed based on available funding.

IV.4 Statistical Design
See Section 9.7.

APPENDIX V: COG STEM CELL COMMITTEE CONSENSUS GUIDELINES FOR ESTABLISHING ORGAN STAGE AND OVERALL GRADE OF ACUTE GRAFT VERSUS HOST DISEASE (GVHD)

Reporting Requirements for Acute GvHD in COG Studies

In an attempt to standardize reporting of acute GvHD, the COG Stem Cell Transplantation Committee has adopted a modification of guidelines that were originally developed at the University of Michigan.

Table 1 outlines standard criteria for GvHD organ staging. However, confounding clinical syndromes (such as non-GvHD causes of hyperbilirubinemia) may make staging GvHD in a given organ difficult. In addition, timing of organ specific symptoms affects whether that symptom is more or less likely to be true GvHD. Please refer to ***Tables 2 and 3*** to assist you in deciding whether to attribute these clinical findings to GvHD, especially in situations where a biopsy is not possible. For additional help, please see the text which follows the tables. ***Table 4*** reviews the approach to assessing GvHD as acute, chronic, or the overlap between the two.

Finally, *engraftment syndrome* will be reported separately from the GvHD scoring presented below.

Engraftment Syndrome

A clinical syndrome of fever, rash, respiratory distress, and diarrhea has been described, just prior to engraftment in patients undergoing unrelated cord blood and mismatched transplantation. If, in the judgment of the local investigator, a patient experiences this syndrome, details of the event should be reported when requested in the study CRFs.

Modified Glucksberg Staging Criteria for Acute Graft versus Host Disease

Table 1 Organ Staging (See tables and text below for details)

Stage	Skin	Liver (bilirubin)	Gut (stool output/day)
0	No GvHD rash	< 2 mg/dL	Adult: < 500 mL/day Child: < 10 mL/kg/day
1	Maculopapular rash < 25% BSA	2-3 mg/dL	Adult: 500–999 mL/day Child: 10 -19.9 mL/kg/day ***Or persistent nausea, vomiting, or anorexia, with a positive upper GI biopsy.***
2	Maculopapular rash 25 – 50% BSA	3.1-6 mg/dL	Adult: 1000-1500 mL/day Child: 20 – 30 mL/kg/day
3	Maculopapular rash > 50% BSA	6.1-15 mg/dL	Adult: > 1500 mL/day Child: > 30 mL/kg/day
4	Generalized erythroderma plus bullous formation and desquamation > 5% BSA	>15 mg/dL	Severe abdominal pain with or without ileus, or grossly bloody stool (regardless of stool volume).

For GI staging: The "adult" stool output values should be used for patients > 50 kg in weight. Use 3 day averages for GI staging based on stool output. If stool and urine are mixed, stool output is presumed to be 50% of total stool/urine mix (see Section 3.2).

For stage 4 GI: the term "severe abdominal pain" will be defined as:
(a) Pain control requiring institution of opioid use, or an increase in on-going opioid use, PLUS
(b) Pain that significantly impacts performance status, as determined by the treating MD.

If colon or rectal biopsy is +, but stool output is < 500 mL/day (< 10 mL/kg/day), then consider as GI stage 0.

There is no modification of liver staging for other causes of hyperbilirubinemia

Overall Clinical Grade (based on the highest stage obtained):
Grade 0: No stage 1-4 of any organ
Grade I: Stage 1-2 skin and no liver or gut involvement
Grade II: Stage 3 skin, or Stage 1 liver involvement, or Stage 1 GI
Grade III: Stage 0-3 skin, with Stage 2-3 liver, or Stage 2-3 GI
Grade IV: Stage 4 skin, liver or GI involvement

Table 2 Evaluating Liver GvHD in the Absence of Biopsy Confirmation (See Table 3.0 below)

Establishing liver GvHD with no skin or GI GvHD

No Skin/GI GvHD Day 0-35	**Assume no liver GvHD,** unless proven by biopsy	
No Skin/GI GvHD Day 36-100	If NO other etiology identified, NO improvement with stopping hepatotoxic medications/TPN: **Stage as liver GvHD**	If other etiology identified or improves with stopping hepatotoxic drugs/TPN: **Do not stage as liver GvHD**

Establishing liver GvHD with skin or GI GvHD and other cause of hyperbilirubinemia

Skin and/or GI GvHD present	Worsening bilirubin level (includes worsening just prior to onset of skin or GI tract GvHD) OR stable elevated bilirubin despite resolution of non-GvHD cause of increased bilirubin: **Stage as liver GvHD**	Stable or improving bilirubin after diagnosis of skin or GI GvHD, irrespective of treatment: **Do not stage as liver GvHD**

Changing liver GvHD stage with other cause of hyperbilirubinemia

Skin and GI GvHD stable, improving, or absent	Liver GvHD staging is carried forward without increase in stage until other disease process resolves (e.g., if TTP is diagnosed in the presence of stage 2 liver GvHD, the liver GvHD stage 2 is carried forward despite rising bilirubin level until TTP is resolved. If there is no liver GvHD – stage 0 – and new onset TTP, the stage 0 is carried forward until TTP is resolved).

Skin and/or GI GvHD worsening	**Liver GvHD is staged according to the Glucksberg criteria. The elevated bili is attributed to GvHD alone.** Thus, when skin or GI GvHD is worsening, there is no downgrading of liver GvHD staging for other causes of hyperbilirubinemia. (e.g., if TTP is diagnosed in the presence of stage 2 liver GvHD and worsening skin or GI GvHD, the liver is staged according to the actual bilirubin level even if some of the rise in bilirubin is attributed to TTP). Similarly, even if there is no liver GvHD at onset of a new process, (such as TPN cholestasis), but skin or GI GvHD worsen during that process, then liver GvHD is diagnosed and staged according to the height of the bilirubin. **There is one exception to this**: the diagnosis of TTP, with high LDH and **unconjugated** bilirubin precludes the diagnosis and staging of new liver GvHD in the absence of a confirmatory liver biopsy.

Table 3 Evaluating GI GvHD in the Absence of Biopsy Confirmation (See Table 4.0 below)

Establishing GI GvHD with new onset diarrhea and no skin or liver GvHD

No Skin/liver GvHD Day 0 through engraftment	Assume no GI GvHD, unless proven by biopsy	
No Skin/liver GvHD Engraftment through day 100	NO other etiology of diarrhea identified: **Stage as GI GvHD**	Any other etiology of diarrhea identified: **Do not stage as GI GvHD**

Establishing GI GvHD with pre-existing diarrhea and skin or liver GvHD

Skin and/or liver GvHD present	Worsening diarrhea (includes worsening just prior to onset of skin or liver GvHD) OR persistent diarrhea despite resolution of non-GvHD cause: **Stage as GI GvHD**	Improving diarrhea after the diagnosis of skin or liver GvHD (irrespective of treatment) OR persistent diarrhea without resolution of underlying non-GvHD cause: **Do not stage as GI GvHD**

Differentiating Acute GvHD, Chronic GvHD, and Overlap Syndrome

There is often confusion differentiating acute from chronic GvHD, especially in the setting of reduced intensity transplants, DLI and new prophylactic treatments. The NIH Working Group recently published new classifications for GvHD:

Table 4 Acute GvHD, Chronic GvHD, and Overlap Syndrome

Category	Time of Symptoms after HCT or DLI	Presence of Acute GvHD features	Presence of Chronic GvHD features
Acute GvHD			
Classic acute GvHD	≤100 d	Yes	No
Persistent, recurrent, or late-onset acute GvHD	>100 d	Yes	No
Chronic GvHD			
Classic chronic GvHD	No time limit	No	Yes
Overlap syndrome	No time limit	Yes	Yes

- Scoring of acute GvHD may need to occur past day 100. In particular, patients should continue to be scored for acute GvHD when classic acute GvHD symptoms (maculopapular rash, nausea, vomiting, anorexia, profuse diarrhea - particularly if bloody and ileus) persist past day 100 or if identical symptoms previously scored as acute GvHD resolve and then recur within 30 days during immunosuppression taper but past day 100.
- Those patients being scored as having acute GvHD should NOT have diagnostic or distinctive signs of chronic GvHD.
- **Patients with both acute and chronic symptoms should be diagnosed as having Overlap Syndrome and scored according to their chronic GvHD score**.

Further Explanation of Criteria presented in Tables 2 and 3.

1.0 Assessment of Skin GvHD

1.1 Presence or Absence of Skin GvHD: Skin GvHD will be considered present if a rash characteristic of acute GvHD develops after allogeneic marrow transplantation involving more than 25% of the body surface not clearly attributable to causes such as drug administration or infection. The extent of the body surface area involved can be estimated by the "Rule of Nines". In estimating the extent of skin GvHD, the area involved is calculated for individual anatomic areas, such as the arm or leg, and then the total is derived from a simple summation. Areas that are non-blanching should not be considered involved regardless of the overlying color of the rash (red, brown, etc.). Limited distribution erythema (with the exception of palms and soles) in the absence of associated rash elsewhere on the body will not be considered GvHD.

2.0 Assessment of Liver GvHD

2.1 Assessing for the Presence or Absence of Liver GvHD

A. Hyperbilirubinemia (total bilirubin ≥ 2.0 mg/dL) in the **absence** of other signs of acute GvHD in the skin or GI tract:

i) Day 0-35: If hyperbilirubinemia alone is present with no other signs of acute GvHD in other organ systems, acute GvHD will not be diagnosed based solely on laboratory abnormalities. Acute GvHD will be diagnosed if findings on histopathology studies of liver from a biopsy or autopsy are confirmatory.

ii) Day 35-100: If hyperbilirubinemia (must be conjugated bilirubin) is not improving or is exacerbated (especially if serum alkaline phosphatase is increased), in the absence of acute GvHD in other organ systems, no other etiologies are identified, and does not improve with discontinuation of hepatotoxic drugs, acute GvHD will be diagnosed. However, it is distinctly unusual to develop ascites or a coagulopathy in the early stages

of acute GvHD of the liver alone. In the absence of histopathology studies of liver from a biopsy or autopsy specimen, ascites or a coagulopathy secondary to liver dysfunction will be considered to indicate the presence of another disease process (e.g. veno-occlusive disease). Recommended non-invasive studies to define an etiology for hyperbilirubinemia are:

a. Imaging of liver (CT or ultrasound)
b. Hepatitis screen (only if ALT is elevated)
c. PT
d. Blood cultures
e. Review of medication list for potentially hepatotoxic drugs
f. Review of risk factors for viral liver infection (HSV, CMV, VZV, adenovirus, EBV, HBV, and HCV)
g. Hemolysis screen

B. Pre-existing hyperbilirubinemia clearly attributed to an etiology other than acute GvHD in the presence of signs of acute GvHD in other organ systems.
   i) If pre-existing non-GvHD liver disease (documented clinically, by lab assessment, or by imaging studies) is stable or improving at the onset of signs of acute GvHD in other organs, then acute GvHD of the liver will not be considered to be present unless proven by liver biopsy or autopsy.
   ii) If hyperbilirubinemia worsens several days before or at the time of onset of signs of acute GvHD in other organ systems, GvHD will be considered to be present unless histopathology studies of liver are available and negative on a biopsy during that time interval or autopsy results exclude GvHD.
   iii) If hyperbilirubinemia persists and is not improving after resolution of a pre-existing non-GvHD liver disease process (e.g. localized infection of liver, systemic sepsis, biliary tract obstruction) when signs of acute GvHD are present in other organ systems or no other intervening cause has been diagnosed, then acute GvHD will be considered to be present in the absence of a new, clearly identifiable cause of non-GvHD liver disease or unless a liver biopsy or autopsy specimen is negative.

C. Prior acute GvHD in liver with new onset of a disease process that exacerbates pre-existing or recently resolved hyperbilirubinemia:
   i) If an etiology other than acute GvHD is clearly identified as causing or exacerbating hyperbilirubinemia and acute liver GvHD has been diagnosed and has been stable, improving, or resolved, then the liver will not be restaged for acute GvHD until the resolution or stabilizing of the concurrent disease process (i.e., the liver stage prior to the onset of the new disease process will be carried forward until the new disease process resolves). Example: Acute GvHD of the liver and gut is diagnosed on day 20. Treatment of acute GvHD results in falling bilirubin levels to liver stage 1. Sepsis or TTP develops with transient worsening of the hyperbilirubinemia. The liver stage is not increased, despite a higher bilirubin level, because the cause of worsening hyperbilirubinemia is attributed to sepsis or TTP.
   ii) If an etiology other than acute GvHD is clearly identified as causing or exacerbating hyperbilirubinemia in the presence of already worsening acute liver GvHD **or** GvHD of the skin or GI tract is simultaneously worsening, then the liver GvHD will be staged according to the actual bilirubin level, even though another cause of hyperbilirubinemia is present.

3.0 Assessment of GvHD of the Gastrointestinal Tract

3.1 Assessing for the Presence or Absence of GvHD of the Gastrointestinal Tract

A. Diarrhea (≥ 500 mL/day in adults or > 10 mL/kg in pediatric patients) in the absence of other signs of acute GvHD in other organ systems
   i) Day 0-engraftment: If diarrhea alone is present without other signs of acute GvHD in other organ systems, acute GvHD will not be considered present. Diarrhea will be attributed to

acute GvHD if histopathology studies of gastrointestinal tract from a biopsy or autopsy are diagnostic.

ii) Engraftment-Day 100: If diarrhea persists and is not improving, is exacerbated, or develops de novo in the absence of acute GvHD in other organ systems, histopathology studies of gut biopsies or from autopsy specimens are not available, and no other etiologies are clearly identified, acute GvHD will be considered to be the cause. A stool specimen should be examined to rule out infectious causes (e.g. rotavirus, adenovirus, and C. difficile toxin). It is recommended, if at all possible, that biopsies be obtained for diagnostic purposes.

B. Pre-existing diarrhea clearly attributed to an etiology other than acute GvHD in the presence of signs of acute GvHD in other organ systems:

i) If pre-existing diarrhea caused by a process other than GvHD has been documented clinically or by lab assessment and is stable or improving at the onset of signs of acute GvHD in the skin or liver, then acute GvHD of the intestine will not be considered to be present in the absence of biopsy confirmation or autopsy report.

ii) If diarrhea or gastrointestinal symptoms are already present, but worsen significantly at the time of onset of signs of acute GvHD in the skin or liver, GvHD will be considered present, unless biopsy or autopsy are negative.

iii) If diarrhea persists after resolution of a pre-existing disease process with signs of acute GvHD present in other organ systems, GvHD will be considered present, unless biopsy or autopsy are negative.

C. Prior or present acute GvHD in other organ systems with new onset of diarrhea:

If diarrhea is **clearly** attributable to an etiology other than acute GvHD (e.g., infection) and a history of acute GvHD exists or acute GvHD is present in other organ systems and is stable, then the gastrointestinal tract will not be evaluable for acute GvHD until the resolution or stabilizing of the other disease process (e.g., infection) in the absence of biopsy or autopsy confirmation.

D. Persistent anorexia, nausea or vomiting in the absence of signs of acute GvHD in other organ systems:

Persistent anorexia, nausea or vomiting in the absence of other known causes of these symptoms will be considered stage 1 acute GvHD if confirmed by endoscopic biopsy.
If a biopsy is not possible (e.g. secondary to thrombocytopenia) but clinical findings are compatible with acute GvHD, then the patient will be treated and recorded as having acute GvHD.

3.2 Staging of the Gastrointestinal Tract for the Severity of Acute GvHD

The severity of gastrointestinal tract GvHD will be staged according to modified Glucksberg criteria. To minimize errors caused by large day-to-day variation, diarrhea volume is measured as an average over 3 days and reported as the volume in milliliters per day. When urinary mixing is noted the stool volume will be considered half of the total volume unless nursing staff is able to give a better estimate from direct observation. Abdominal cramps are considered significant for staging if the severity results in a clinical intervention (e.g. analgesia, fasting, etc.). Blood in the stools is considered significant if the blood is visible or hematochezia/ melena is present and not clearly attributed to a cause other than GvHD (e.g. epistaxis/ hemorrhoids).

APPENDIX VI: POSSIBLE DRUG INTERACTIONS

Some drugs, food, and supplements may interact with rituximab (or biosimilar). Examples include:

Drugs that may interact with rituximab (or biosimilar)*

• Arthritis medications
  • Leflunomide, tofacitinib
• Heart or high blood pressure medications
  • Amlodipine, atenolol, captopril, carvedilol, clonidine, enalapril, lisinopril, metoprolol, nicardipine, propranolol, sotalol
• Other medications
  • Abatacept, abciximab, baricitinib, belimumab, certolizumab pegol, clozapine, deferiprone, natalizumab

Food and supplements that may interact with rituximab (or biosimilar)**
• Echinacea

**Sometimes these drugs are used with rituximab (or biosimilar)on purpose. Discuss all drugs with your doctor.*

***Supplements may come in many forms, such as teas, drinks, juices, liquids, drops, capsules, pills, or dried herbs. All forms should be avoided.*

The list above does not include everything that may interact with your chemotherapy. Talk to your doctor before starting any new medications, over-the-counter medicines, or herbal supplements and before making a significant change in your diet.

APPENDIX VII: YOUTH INFORMATION SHEETS

INFORMATION SHEET REGARDING RESEARCH STUDY ANHL1522
(for children from 7 through 12 years of age)

A study of a drug (Rituximab) and cells (LMP-TC) to treat PTLD

1. We have been talking with you about your tumor. The kind of tumor you have is called PTLD. PTLD happens when a type of white blood cell that fights infection does not grow normally. After doing tests, we have found that you have this type of tumor.

2. We are asking you to take part in a research study because you have PTLD. A research study is when doctors work together to try out new ways to help people who are sick. The goal of this study is to learn more about how to treat PTLD and reduce the bad effects of drugs used to treat PTLD.

3. If you are newly diagnosed with PTLD or if the PTLD has relapsed (come back) you will receive a drug called rituximab. Then some children will get a therapy called LMP-specific T cells (LMP-TC). LMP-TC is made from another person's cells in order to help the immune system fight the PTLD. The treatment you get will depend on how well the rituximab works, and if enough LMP-TC doses are ready. Your doctor will tell you whether you will receive LMP-TC therapy.

4. If you have PTLD that hasn't responded to treatment with rituximab prior to taking part of this study, you will get the therapy called LMP-TC.

5. You will have regular tests during your treatment. These tests help doctors to decide the best treatment for you and to see how you are doing with treatment. We will take samples of blood for the study. These samples would be taken when other standard blood tests are being done, so there would be no extra blood draws.

6. Sometimes good things can happen to people when they are in a research study. These good things are called "benefits." We hope that a benefit to you of being part of this study is getting rid of the PTLD for as long as possible, and with fewer bad effects but we don't know for sure if there is any benefit of being part of this study.

7. Sometimes bad things can happen to people when they are in a research study. These bad things are called "risks." The risks to you from this study are that you will have more bad effects with the rituximab or LMP-TC than you would with the usual medicines. We do not know this for sure which is why we are doing this study. Other things may happen to you that we don't yet know about.

8. Your family can choose to be part of this study or not. Your family can also decide to stop being in this study at any time once you start. There may be other treatments for your illness that your doctor can tell you about. Make sure to ask your doctors any questions that you have and talk with your family as they are making this decision.

9. We are asking your permission to collect additional blood. We want to see if there are ways to tell how the PTLD will respond to treatment. These samples would be taken when other standard blood tests are being performed, so there would be no extra blood draws. You can still take part in this study even if you don't allow us to collect the extra blood samples for research.

INFORMATION SHEET REGARDING RESEARCH STUDY ANHL1522
(for teens from 13 through 17 years of age)

A Study of Rituximab and LMP-specific T cells (LMP-TC) to Treat Post-Transplant Lymphoproliferative Disease (PTLD).

1. We have been talking with you about your Post-Transplant Lymphoproliferative Disease (PTLD). PTLD is a type of tumor of the immune system. PTLD happens when a type of white blood cell that fights infection does not grow normally. Sometimes this abnormal growth is caused by a virus called Epstein-Barr virus (EBV). After doing tests, we have found that you have this type of tumor.

2. We are asking you to take part in a research study because you have PTLD. A research study is when doctors work together to try out new ways to help people who are sick. The goal of this study is to learn more about how to better treat PTLD and to reduce the bad effects of the drugs used to treat PTLD.

3. If you are newly diagnosed with PTLD or if the PTLD has relapsed (come back after treatment) you will first be treated with a drug called rituximab. Then some children will get an immune cell therapy called LMP-specific T cells (LMP-TC). The LMP-TC doses are made from another person's cells in order to help the immune system fight the PTLD by targeting the EBV infected tumor cells. The treatment you get will depend on how well the rituximab works and whether enough LMP-TC doses are matched and available. Your doctor will tell you whether you will receive LMP-TC therapy.

4. If you have PTLD that hasn't responded to treatment with rituximab prior to taking part of this study, you will get the therapy called LMP-TC.

5. You will have regular tests during your treatment. These tests help doctors in deciding the best treatment for your PTLD and to see how you are doing with treatment. We will take samples of blood to study the response to treatment. These samples would be taken when other standard blood tests are being performed, so there would be no extra blood draws.

6. Sometimes good effects can happen to people when they are in a research study. These good things are called "benefits." We hope that a benefit to you of being part of this study is getting rid of the PTLD for as long as possible, and with fewer side effects from the treatment. But we don't know for sure if there is any benefit of being part of this study.

7. Sometimes effects that are not helpful and might be harmful or negative can happen to people when they are in a research study. These negative effects are called "risks." The risks to you from this study are that you will have more bad side effects with the study medicines than you would with the medicines that are usually given for PTLD. We do not know this for sure which is why we are doing this study. Other things may happen to you that we don't yet know about.

8. Your family can choose for you to be a part of this study or not. Your family can also decide for you to stop being in this study at any time once you start. There may be other treatments for your illness that your doctor can tell you about. Make sure to ask your doctors any questions that you have and talk with your family as they are making this decision.

9. We are asking your permission to collect additional blood. We want to see if there are ways to tell how the PTLD will respond to treatment. These samples would be taken when other standard blood tests are being performed, so there would be no extra blood draws. You can still be treated on this study even if you don't allow us to collect the extra blood samples for research.

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