LOI CONSENSUS REVIEW RESPONSE

Observational Cohort Study of People Living with HIV Treated with CD19-Directed CAR T Cell Therapy for B-Cell Lymphoid Malignancies

Version 1.0

NCI Protocol #: AMC-113
Local Protocol #: AMC-113

NCI Version Date: 27APR2021
Protocol Date: 27APR2021

I. Comments Requiring a Response – Major Issues:

#	Section	Comments
1.	Global	CTEP did not understand the proposal. NCI funds the CIMBTR and the CIDR for collection of these data. This appears to involve funding work for duplicative efforts already funded. Has contact with CIDR been made by AMC to discuss opportunities? An OEWG call will be scheduled to discuss. **Preliminary Response to CTEP Review:** Our proposal has been discussed both the CIBMTR as well the CIDR, which is operated by the CIBMTR. At present (as of 01/12/2021), **the CIBMTR and CIDR do NOT collect HIV status** and/or information on HIV for patients undergoing CAR T cell therapy. **Therefore, it is currently not possible for the CIBMTR and/or CIDR to identify patients with HIV who have undergone CAR T cell therapy,** or provide HIV-related information for any CAR T cell treated patients as HIV forms are currently also not prospectively collected for patients treated with CAR T cell therapy. These facts underpin the importance and rationale for our proposal, where the proposed collaboration will allow a) the AMC to collect data on patients within the AMC network, who have undergone CAR T cell therapy and were not reported to the CIBMTR; and b) identify patients with HIV, who have undergone CAR19 therapy within and outside of the AMC network and who have been reported to the CIBMTR, to the CIBMTR. For patients whose data has been collected by the CIBMTR, no duplicative data collection will occur as currently HIV forms are not collected by the CIBMTR and/or CIDR for patients receiving CAR T cell therapy. The CIBMTR can however contact sites with identified patients to retrospectively complete their standard HIV case report forms, that are otherwise being utilized to collect HIV relevant information on patients receiving non-CAR T cellular therapy. This information in turn will be shared with the AMC as outlined in our proposal. Furthermore, as of January 22, 2021, HIV forms will

		be routinely collected by the CIBMTR for CAR T cell therapy treated patients identified as HIV+. The proposed collaboration between the AMC and CIBMTR therefore is complimentary and promotes synergy. The concerted effort will allow analysis of outcomes for PLWH treated with CD19 CAR T cell therapy outside of clinical trials in a timely fashion, and enable us to fill a glaring knowledge gap, that may prevent PLWH from receiving this life saving treatment outside of a clinical trial while the prospective AMC-112 trial is being conducted. ***<u>January 05, 2021 Conference Call Decision:</u> The CTEP leadership and Study Team discussed in detail the objective of the protocol and the role of the CIBMTR and CIDR for collection of data and the related funding concerns. CTEP agreed that the justification provided in the response above is reasonable and decided that the LOI will be re-reviewed at PRC now that they have better understanding of the overall protocol.*** **<u>PI Response: The protocol team appreciates CTEP's approval to proceed and has clarified the relationships between these groups and the rationale for the trial in Section 2.0 of the protocol.</u>**
2.	Global	CTEP PRC approved the proposal to ascertain potential HIV+ cases from treating sites that may also be in the CIDR/CIBMTR database as proposed for the purposes of evaluating toxicity and other outcomes. Issues to consider is the RAVE build to meet CTEP requirements for utilization of the NCI CIRB. Since this is a non-treatment study, use of the NCI CIRB is not required. **<u>PI Response:</u> The AMC acknowledges CTEP's confirmation that NCI CIRB review will not be required for this protocol. The AMC will comply with any requirements or requests for information to confirm that the trial qualifies as exempt research under 45 CFR 46.104(d)(4)(ii). The trial will involve secondary research for which informed consent is not required, as this involves the use of deidentified health information in the CIBMTR's Cellular Therapy Registry. Participant information in this database is collected from participants who consent to include their data in the Cellular Therapy Registry. The AMC's use of this information for this protocol will involve the use of health information that is recorded by the reporting clinical centers in such a manner that the identity of the human subjects cannot readily be ascertained directly or through identifiers linked to the subjects. The CIBMTR and the clinical site contributing data to the CIBMTR will not contact the subjects, and the CIBMTR will not re-identify subjects for the required analysis. As all data is being collected and analyzed by the CIBMTR using their existing**

		registry, no separate database will need to be built. All data will be collected through the CIBMTR's current processes and systems. **The AMC will ensure that the group requests the minimum necessary data points on a routine basis from the CIBMTR's database to satisfy any data monitoring requirements stipulated by CTEP. Limited information may be available until the CIBMTR completes its data transfer for all eligible cases and if a more flexible option is possible than DMU light for routine data transmission, the AMC would appreciate the recommendation.**



AIDS MALIGNANCY CONSORTIUM

AMC PROTOCOL # 113:

Observational cohort study of people living with HIV treated with CD19-directed CAR T cell therapy for B-cell lymphoid malignancies

A Trial of the AIDS Malignancy Consortium (AMC)

Sponsored by:	National Cancer Institute Office of HIV and AIDS Malignancy (OHAM)
In Collaboration with:	Center for International Blood and Marrow Transplant Research (CIBMTR)
NCT Registration Number:	TBD
Pharmaceutical Support Provided by:	N/A (secondary data analysis only)
Protocol Chair:	Stefan K. Barta, MD, MS
Protocol Co-Chair(s):	Ariela Noy, MD

Version 1.0, April 27, 2021
NCI Version Date April 27, 2021

AMC PROTOCOL SIGNATURE PAGE

I, _____, Principal Investigator at site _____, agree to conduct and follow this protocol: **AMC Protocol #113 – Observational cohort study of people living with HIV treated with CD19-directed CAR T cell therapy for B-cell lymphoid malignancies (Version 1.0, 27APR2021),** as written according to AMC and NCI guidelines, and standards of Good Clinical Practice (GCP, ICH E6 R2). I understand that no deviations from the protocol eligibility criteria or waivers for protocol deviations will be permitted.

_____ _____

Signature Date (DDMMMYYYY)

TABLE OF CONTENTS

LOI CONSENSUS REVIEW RESPONSE ..... **i**
AMC PROTOCOL SIGNATURE PAGE **2**
TABLE OF CONTENTS **3**
LIST OF TABLES AND FIGURES **5**
PROTOCOL ROSTER **6**
PROTOCOL SYNOPSIS **7**
LIST OF ABBREVIATIONS **9**
1.0 OBJECTIVES **11**
1.1 Primary Objective 11
1.2 Secondary Objective 11
1.3 Exploratory Objective 11
2.0 BACKGROUND **12**
2.1 Study Disease 12
2.2 Study Agents 13
2.3 Study Design and Rationale 13
3.0 PARTICIPANT SELECTION **16**
3.1 Eligibility Criteria 16
3.2 Exclusion Criteria 16
3.3 Number of Participants to be Enrolled 16
3.4 Participant Enrollment Procedures 17
5.0 TREATMENT PLAN **18**
6.0 ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS **19**
7.0 PHARMACEUTICAL INFORMATION **20**
8.0 CLINICAL AND LABORATORY EVALUATIONS **21**
8.1 Screening 21
8.2 Enrollment Data Collection 21
8.3 Variables to be Described 21
8.4 Outcomes to be Collected 22
9.0 STATISTICAL CONSIDERATIONS **24**
9.1 Study Design/Endpoints 24
9.2 Sample Size/Accrual Rate 24
9.3 Statistical Analysis 25

9.4 Analysis of Primary Endpoints 25
9.5 Analysis of Secondary Endpoints 25
9.6 Analysis of Exploratory Endpoints 25
10.0 ROLE OF DATA MANAGEMENT AND DATA REPORTING 27
10.1 CRF Instructions 27
10.2 Data Quality 27
10.3 Data Monitoring 27
11.0 ETHICAL AND REGULATORY CONSIDERATIONS 28
11.1 IRB Exemption Justification 28
11.2 Changes to the Protocol 28
11.3 Women and Minorities 28
12.0 REFERENCES 30

LIST OF TABLES AND FIGURES

Table 1: List of variables included in the data collection 14

Table 2: CTCAE Grading Guidelines 19

Table 3: Estimated 95% confidence intervals for ≥G3 CRS or ICANS based on number of enrolled participants 25

Table 4: Accrual Targets 28

Figure 1: Study workflow 14

PROTOCOL ROSTER

AMC Protocol #113

Observational cohort study of people living with HIV treated with CD19-directed CAR T cell therapy for B-cell lymphoid malignancies.

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PROTOCOL SYNOPSIS

Title:	Observational cohort study of people living with HIV treated with CD19-directed CAR T cell therapy for B-cell lymphoid malignancies
Phase of Study:	Non-interventional – observational cohort study
Accrual Target:	10-30 participants (approximately 2 participants/month)
Population:	The AMC will collaborate with the Center for International Blood and Marrow Transplant Research (CIBMTR) for identification of eligible cases reported to the CIBMTR's registry. This includes participants with documented history of HIV infection and who received CD19-directed CAR T cell therapy for acute lymphoblastic leukemia, diffuse large B-cell lymphoma, high-grade B-cell lymphoma, transformed follicular lymphoma, primary mediastinal B-cell lymphoma, mantle cell lymphoma and follicular lymphoma between August 30, 2017 (date of FDA approval of first commercial CAR19 therapy) and one year after the activation date of this protocol.
Regimen:	Non-interventional. Participant data will be collected for up to 12 months post CAR19 therapy and can be collected prospectively or retrospectively. All data points and variables are readily available and collected as part of standard of care treatment, and will be reported through the CIBMTR's Cellular Therapy Registry.
Anticipated Trial Duration:	Up to 24 months (12 months for case identification, plus up to 12 months for subsequent follow-up data collection by the CIBMTR).
Primary Objective:	The primary objective of this study will be to characterize: • the safety profile of commercial CAR19 therapy in PLWH. • the efficacy of commercial CAR19 therapy in PLWH.
Secondary Objectives:	• To determine lymphoma-specific outcomes in PLWH receiving commercial CAR19 therapy. • To characterize the HIV- and lymphoma specific clinical characteristics of participants. • To assess the impact of CAR19 therapy on HIV disease and immune reconstitution.

Exploratory Objectives:	To identify participant, disease and/or treatment characteristics that are associated with CAR19 therapy related clinical outcomes.

LIST OF ABBREVIATIONS

ACSR	AIDS and Cancer Specimen Resource
ADL	Activities of Daily Living
AE	Adverse Event
AIDS	Acquired Immunodeficiency Syndrome
AMC	AIDS Malignancy Consortium
ANC	Absolute Neutrophil Count
ART	Antiretroviral Therapy
ASTCT	American Society for Transplantation and Cellular Therapy
B-NHL	B-cell Non-Hodgkin Lymphoma
CAR19	CD19-directed Chimeric Antigen Receptor T cells
CBC	Complete Blood Count
CDC	Centers for Disease Control and Prevention
CDUS	Clinical Data Update System
CIBMTR	Center for International Blood and Marrow Transplant Research
CIDR	Cellular Immunotherapy Data Resource
CIOMS	Council for International Organizations of Medical Sciences
CR	Complete Response
CRF	Case Report Form
CRS	Cytokine Release Syndrome
CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
CTEP-AERS	Cancer Therapy Evaluation Program Adverse Event Reporting System
DFS	Disease-Free Survival
DHHS	Department of Health and Human Services
DMU	Data Mapping Utility
DNA	Deoxyribonucleic Acid
DSMB	Data and Safety Monitoring Board
ECOG	Eastern Cooperative Oncology Group
FDA	Food and Drug Administration
HCT-CI	Hematopoietic Cell Transplant Comorbidity Index
HIV	Human Immunodeficiency Virus

ICANS	Immune Effector Cell-Associated Neurotoxicity
IEC	Institutional Ethics Committee
IRB	Institutional Review Board
IND	Investigational New Drug
KPS	Karnofsky Performance Score
LLT	Lowest Level Term
NCI	National Cancer Institute
NRM	Non-Relapse Mortality
NSAIDs	Non-steroidal Anti-inflammatory Drugs
ODMC	Operations and Data Management Center
OS	Overall Survival
PCR	Polymerase Chain Reaction
PFS	Progression Free Survival
PLWH	Persons Living With HIV infection
PR	Partial Response
RCR	Registration and Credential Repository
REB	Research Ethics Board
RNA	Ribonucleic Acid
R/R	Relapse or Refractory
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
TNF	Tumor Necrosis Factor

1.0 OBJECTIVES

1.1 Primary Objective

The primary objective of this study will be to characterize:

- the safety profile of commercial CAR19 therapy in PLWH.
- the efficacy of commercial CAR19 therapy in PLWH.

1.2 Secondary Objective

1.2.1 To determine lymphoma-specific outcomes in PLWH receiving commercial CAR19 therapy.

1.2.2 To characterize the HIV- and lymphoma specific clinical characteristics of participants.

1.2.3 To assess the impact of CAR19 therapy on HIV disease and immune reconstitution.

1.3 Exploratory Objective

1.3.1 To identify participant, disease and/or treatment characteristics that are associated with CAR19 therapy related clinical outcomes.

2.0 BACKGROUND

2.1 Study Disease

Two landmark trials have led to the FDA approval of two different CD19 -directed chimeric antigen receptor (CAR) T cell (CAR19) products in the United States for the treatment of relapsed or refractory (RR) large B-cell lymphoma after two or more lines of systemic therapy: tisagenlecleucel (Kymriah™) and axicabtagene ciloleucel (Yescarta®).(1, 2) In the ZUMA-1 registration trial for axicabtagene ciloleucel (axi-cel), 42% of the 101 treated patients achieved a complete response (CR), and with a median follow up of 15 months, the projected 1-year progression free survival (PFS) was 70%.(2) In a recent updated analysis, the CR rate was 58% with about 40% of patients having durable remissions at 2 years of follow up.(3) Similar results were seen in the JULIET registrational trial for tisagenlecleucel (tisa-cel) with an overall response rate (ORR) of 52%, and a CR rate of 40% in the 93 patients evaluable for response; with a median follow up of 14 months, the estimated 12-months relapse-free survival was 65% (79% among patients with a CR).(1) Tisagenlecleucel is also approved for the treatment of acute B-lineage lymphoblastic leukemia in patients up to the age of 25 years. Two other anti-CD19 CAR T cell products have since been approved, KTE-X19 or brexucabtagene autoleucel (Tecartus ™) has since in mantle cell lymphoma and lisocabtagene maraleucel for (Breyanzi) for relapsed or refractory large B-cell lymphoma.(4, 5) Lastly, axi-cel has also received FDA approval for third-line therapy of follicular lymphoma based on the ZUMA-5 trial.(6) Unfortunately, in none of the trials patients with known HIV infection were included. Therefore, no safety or efficacy data for treatment with CAR19 in people living with HIV (PLWH) exists, and access for PLWH in the US to this potentially curative treatment has been limited.

This has to be contrasted with the fact that malignancies, and specifically lymphomas, remain a major contributor to early mortality in PLWH. With a lifetime risk of cancer ranging between 24-40%, the leading cause of death in PLWH in economically developed countries is cancer, and the most common cancer in PLWH in the US remains Non-Hodgkin lymphoma (NHL).(7-9) While early during the HIV epidemic, outcomes for PLWH and aggressive B-cell lymphomas were significantly worse compared to immunocompetent patients, this is no longer the case for the majority of PLWH, owing mainly to effective antiretroviral therapies leading to better tolerance of myelosuppressive chemotherapy.(10, 11) It has been repeatedly demonstrated that PLWH have been able to safely tolerate aggressive high-dose chemotherapy, as well as autologous and even allogeneic hematopoietic cell transplant.(12, 13) Based on this data, the AMC is poised to conduct a prospective interventional study of axicabtagene ciloleucel in PLWH with relapsed or refractory B-cell lymphoma (AMC-112) to demonstrate the feasibility of CAR19 therapy.

The feasibility of CAR19 is underpinned by recent case reports of 3 patients with HIV who received commercial CAR T cell therapy.[6,7] All 3 patients responded to CAR19 treatment (2 achieved a CR, 1 achieved a “sustained remission”) and none experienced significant CAR19 related toxicities, including immune effector cell mediated cytokine release syndrome (CRS) or neurotoxicity. Notably, all patients had CD4 counts prior to CAR19 therapy of <200 copies/ mm^3 (50 cells/mm^3; 127 cells/mm^3 & 127 cells/mm^3). In addition to these case reports, several institutions (University of Pennsylvania, Memorial Sloan

Kettering, University of California, San Diego; personal communications with Dr. Ariela Noy and Dr. Erin Reid) have successfully treated PLWH with commercial CAR19 product. Outside of this anecdotal experience, however, it remains at this point in time unclear whether CAR19 therapy in patients infected with HIV (or other conditions that result in impaired immune function) is: 1) as efficacious as in immunocompetent patients, and 2) associated with a higher risk of complications related to lymphodepleting conditioning or immune effector cell mediated toxicities. Furthermore, in addition to the possible impact of HIV disease on CAR T cell therapy-related outcomes, the effects of CAR T cells on HIV disease itself remain unexplored. This study aims to fill this knowledge gap and more formally describe the available experience with CAR19 therapy in PLWH. In this observational prospective cohort study of PLWH who have received or will be receiving CAR19 therapy at institutions participating in the AMC and/or the Center for International Blood and Marrow Transplant Research (CIBMTR), **we will collect available data on CAR19 therapy related outcomes.** We aim to describe and analyze the available "real world" experience of patients treated with CAR19 therapy outside of clinical trials. The thus gained information from this observational cohort of patients treated with commercial CAR19 therapy will provide complimentary information that cannot be obtained from an interventional trial, including data on outcomes in participants who may otherwise fall out of the often strict eligibility criteria mandated for enrollment in clinical trials. Furthermore, insights obtained by studying outcomes in this cohort of patients may help address issues that arise during conduct of the planned interventional trial. For the CAR19 observational cohort, the AMC will collaborate with other non-AMC institutions participating in the CIBMTR.

We hypothesized that CAR19 therapy is safe and effective in patients with well controlled HIV infection similar to non-HIV infected patients.

2.2 Study Agents

This study is observational, so no study agents are administered as part of this protocol.

2.3 Study Design and Rationale

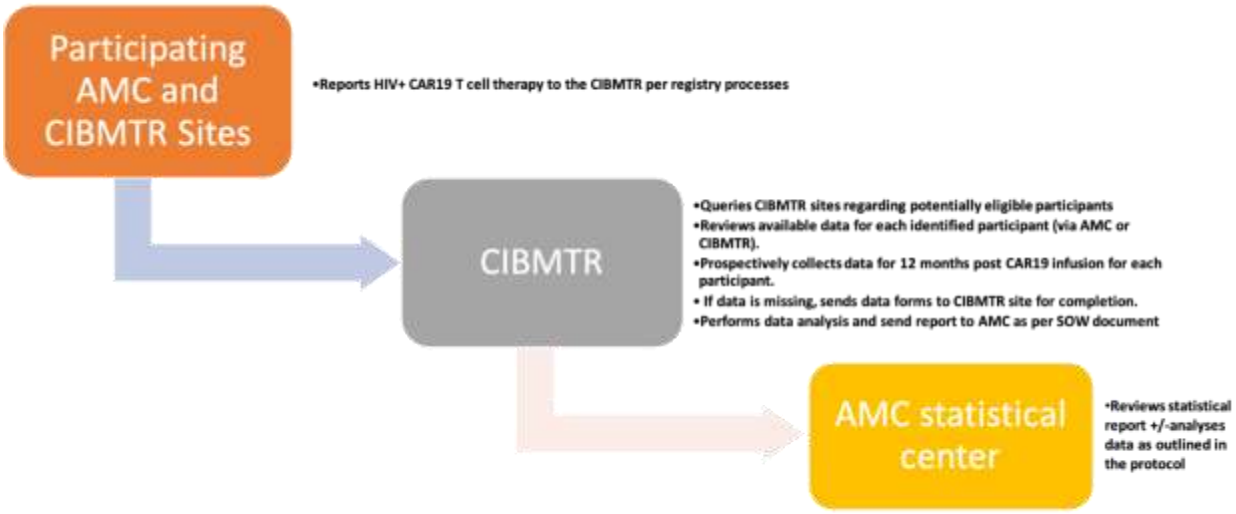
This protocol will develop an observational cohort of PLWH who have been or are being treated with CAR19 therapy outside of the AMC clinical trial AMC-112.

Following approval of this protocol, sites will be asked to identify eligible participants, who carry a diagnosis of HIV disease AND received CAR19 therapy between August 30, 2017 and one year after the activation date for this protocol. The case identification process will occur through the CIBMTR's Cellular Therapy Registry case report forms.

The CIBMTR will query participating CIBMTR sites to identify eligible participants that have received or will receive CAR19 therapy within the proposed study period. Before January 2021, the CIBMTR did not routinely collect HIV status and HIV-related outcomes from participating sites with patients undergoing cellular therapy with CAR19 cell therapy. However, other treatment and disease relevant data on patients undergoing cellular therapy, including CAR T cell therapy, is being routinely reported and collected at present. For the identified patients, the sites in turn will receive data forms from the CIBMTR to complete and report back to the CIBMTR the HIV-related missing variables (see study workflow in Figure 1). The CIBMTR will thus be able to collect and analyze the variables listed in

Table 1 for PWLH who have been treated with CAR19 within the proposed study period.

Figure 1:Study workflow



Data collection will include the variables listed in Table 1. (please note, that all these data points are available as part of standard of care for participants undergoing CAR19 therapy).

Table 1: List of variables included in the data collection

Category	Data fields
Demographics	Age; sex; race
Participant characteristics	Performance status; comorbidities including hepatitis B or C infection; and Hematopoietic Cell Transplant Comorbidity Index (HCT-CI) prior to CAR19 therapy.
HIV disease	Date of HIV diagnosis; ART regimen at time of CAR19 therapy; past ART regimen(s); history of OI; viral load, CD4 count at time of leukapheresis, 3 months, 6 months and 12 months post CAR19 infusion; occurrence of OI and other infections after CAR19 therapy.
B-cell Malignancy	Type of leukemia/lymphoma; date leukemia/lymphoma first diagnosed; stage at diagnosis; initial treatment; response to initial treatment; date of relapse or progression; treatment at relapse or progression.
CAR19 Treatment	Disease status of leukemia/lymphoma prior to CAR19 therapy; type of CAR19 therapy; time from leukapheresis to product infusion; product cell

Category	Data fields
	dose; type of lymphodepleting therapy; CAR19 product used; toxicity related to CAR19 therapy; time to neutrophil and platelet recovery; response to CAR19 therapy at 3 months and 6 months; date of progression/relapse; disease status at 3 months, 6 months and 12 months post CAR19 therapy.

Participant data will be collected for up to 12 months post CAR19 therapy and can be collected prospectively or retrospectively. All data points and variables are readily available from the medical record as collected during standard of care treatment.

3.0 PARTICIPANT SELECTION

Participant case selection will be performed by the CIBMTR based on records reported by AMC and other CIBMTR sites in the Cellular Therapy Registry. Participant information in this database is collected from participants who consent to include their data in the Cellular Therapy Registry, for a secondary data analysis. The AMC's use of this information for this protocol will involve the use of health information that is recorded by the reporting clinical centers in such a manner that the identity of the human subjects cannot readily be ascertained directly or through identifiers linked to the subjects. The CIBMTR and the clinical site contributing data to the CIBMTR will not contact the subjects further to submit any required data, and the CIBMTR will not re-identify subjects for the required analysis. As such, clinical investigators fulfill the requirement for identifying eligible cases by their existing participation in the CIBMTR. The CIBMTR will supply the AMC the datasets described in Section 8.3 for eligible cases, for the protocol team to perform the analyses described in Section 9.0.

3.1 Eligibility Criteria

____ 3.1.1 HIV positive. Documentation of HIV diagnosis in the Cellular Therapy Registry case report forms;

____ 3.1.2 Participants must have histologically or cytologically confirmed B-cell malignancy. This includes, but is not limited to B-lineage acute lymphoblastic leukemia, diffuse large B-cell lymphoma, primary mediastinal B cell lymphoma, transformed or untransformed indolent B-cell lymphoma (such as follicular lymphoma, marginal zone lymphoma, lymphoplasmacytic lymphoma, small lymphocytic lymphoma), high-grade B-cell lymphoma, Burkitt lymphoma, mantle cell lymphoma, and chronic lymphocytic leukemia.

____ 3.1.3 Age ≥18 years at time of CAR19 infusion. Date of birth and age should be determined based on best possible information or documentation available.

____ 3.1.4 Received CD19-directed CAR T cell therapy for a B-cell lymphoid malignancy between August 30, 2017 (date of FDA approval of first commercial CAR19 therapy) and one year after the activation date of this protocol.

3.2 Exclusion Criteria

Participants who do not fulfill the criteria as listed in Section 3.1 above, are ineligible. Additionally**,** the presence of any of the following conditions will exclude a participant from study enrollment:

____ 3.2.1 Participants who received prior treatment with any other CAR T cell therapy.

____ 3.2.2 Participating in an AMC-led clinical trial of CD19-directed CAR T cell therapy.

3.3 Number of Participants to be Enrolled

NIH policy requires that women and members of minority groups and their subpopulations be included in all NIH-supported biomedical and behavioral research projects involving

NIH-defined clinical research unless a clear and compelling rationale and justification establishes to the satisfaction of the funding Institute & Center (IC) Director that inclusion is inappropriate with respect to the health of the participants or the purpose of the research. Exclusion under other circumstances must be designated by the Director, NIH, upon the recommendation of an IC Director based on a compelling rationale and justification. Cost is not an acceptable reason for exclusion except when the study would duplicate data from other sources. Women of childbearing potential should not be routinely excluded from participation in clinical research. Please see http://grants.nih.gov/grants/funding/phs398/phs398.pdf.

____ 3.3.1 Proposed sample size

This study will enroll a minimum of 10 and a maximum of 30 participants.

Accrual rate

Approximately 2 participants per month.

____ 3.2.3 Distribution by sex, ethnicity

There are no *a priori* determinations concerning the distribution or enrollment of participants according to these characteristics. We expect final enrollment to generally reflect the epidemiology of HIV-associated B-cell lymphomas.

3.4 Participant Enrollment Procedures

All cases selected for this trial must be consented and submitted through the CIBMTR's Cellular Therapy Registry, following their existing processes, protocols, and forms (see https://www.cibmtr.org/DataManagement/ProtocolConsent/ObservationalData/pages/index.aspx for observational database protocol and consent forms). The CIBMTR will provide the AMC-113 protocol team datasets for cases meeting the above-mentioned eligibility criteria for this secondary data analysis. No directly identifying protected health information will be provided to the AMC-113 protocol team.

5.0 TREATMENT PLAN

This is an observational study. No intervention will be administered as part of this protocol. There are no exclusively trial related procedures.

6.0 ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse events (AEs) related to CAR19 therapy is collected as part of the CIBMTR data collection process for up to 12 months post CAR19 therapy and can be collected prospectively or retrospectively. Data forms for adverse event reporting for the CIBMTR's Cellular Therapy Registry are available online at: https://www.cibmtr.org/DataManagement/DataCollectionForms/Pages/index.aspx.

Each CTCAE term in the current version is a unique representation of a specific event used for medical documentation and scientific analysis and is a single MedDRA Lowest Level Term (LLT). Grade is an essential element of the Guidelines and, in general, relates to severity for the purposes of regulatory reporting to NCI as follows:

Table 2: CTCAE Grading Guidelines

Grade	Description
0	No AE (or within normal limits)
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
2	Moderate; minimal, local, or noninvasive intervention (e.g., packing, cautery) indicated; limiting age-appropriate instrumental activities of daily living (ADL)
3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL
4	Life-threatening consequences; urgent intervention indicated
5	Death related to AE

NOTE: A severe AE, as defined by the above grading scale, is NOT the same as serious AE, as defined below (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

7.0 PHARMACEUTICAL INFORMATION

Not applicable (non-interventional study).

8.0 CLINICAL AND LABORATORY EVALUATIONS

8.1 Screening

Following regulatory approval of this protocol, sites will be asked to capture information of participants, who carry a diagnosis of HIV disease AND received CAR19 therapy outside of a clinical trial between August 30, 2017 and one year from protocol activation.

All study relevant data is routinely collected via the CIBMTR data requirements or will be collected via additional data forms sent to the CIBMTR site for identified eligible participants.

8.2 Enrollment Data Collection

Participant data will be collected by the CIBMTR/CIDR for up to 12 months post CAR19 therapy and can be collected prospectively or retrospectively. All data points and variables are readily available from the participant's medical record and collected as part of standard of care treatment.

8.3 Variables to be Described

8.3.1 Recipient-related

- Recipient age at infusion, years
- Recipient sex: male, female
- Recipient race: White, African American or Black, Asian, Native Hawaiian or other Pacific Islander, American Indian or Alaska Native, More than one race.
- Recipient ethnicity: Hispanic or Latino, non-Hispanic nor Latino
- Karnofsky performance status before transplant*: <90, >90, not reported (see Appendix II)
- Hematopoietic Cell Transplantation-specific Comorbidity Index (**HCT-CI**)
- Hepatitis B infection prior to infusion
- Hepatitis C infection prior to infusion
- HCT-CI prior to infusion
- Cause of death

8.3.2 Disease-related

- Date of HIV-diagnosis
- ART regimen at time of infusion
- Past ART regimens
- History of OI
- HIV viral load pre-infusion
- Disease
- Disease status at infusion
- CD4 count at 3 mo, 6 mo & 12 mo post CAR19 therapy
- Infection post infusion
- Date of diagnosis of leukemia/lymphoma
- Disease stage at diagnosis
- Initial treatment
- Response to initial treatment

- Time to relapse/progression
- Treatment at relapse/progression
- Disease status prior to infusion
- Type of CAR19 therapy/product used
- Time from leukapheresis to product infusion
- Product cell dose
- Type of lymphodepleting therapy
- Toxicity related to infusion
- Time to neutrophil and platelet recovery
- Response to infusion therapy at 3 mo and 6 mo
- Disease status (response rate) at 3, 6 and 12 mo post infusion
- CRS; grade by CTCAE and ASTCT criteria

8.4 Outcomes to be Collected

8.4.1 Overall survival (OS): Death from any cause. Time to death starts from the date of CAR19 infusion. Surviving participants are censored at the date of the last contact.

8.4.2 Relapse/Progression: Post-CAR19 recurrence or progression of the primary disease for which CAR19 therapy is performed. This event will be summarized by the cumulative incidence estimate where non-relapse mortality will be treated as the competing risk. The time to the event starts at the date of CAR19 infusion. Participants who survive without relapse/progression will be censored at the date of the last contact.

8.4.3 Non-relapse mortality (NRM): Death in remission (without primary disease relapse/progression). Time to event starts from the date of CAR19 infusion. This event will be summarized by the cumulative incidence estimate where relapse/progression will be treated as the competing risk. Surviving participants will be censored at the date of the last contact.

8.4.4 Disease-free survival (DFS): Events are defined as death or relapse/progression of primary disease. Time to event starts from the date of CAR19 infusion. Participants who are alive and in remission will be censored at date of last contact. There is no competing risk.

8.4.5 Infections post CAR-T

8.4.6 Response rate, includes stable disease, progressive disease, partial response (PR), complete response (CR), and overall response (PR and CR)

8.4.7 Disease status post CAR-T

8.4.8 Toxicity (defined as the occurrence of adverse events) at least possibly related to CAR-T

8.4.9 Neutrophil engraftment

8.4.10 Platelet recovery

8.4.11 CRS and grade by CTCAE and American Society for Transplantation and Cellular Therapy (ASTCT) criteria

8.4.12 ICANS and grade as per ASTCT criteria

9.0 STATISTICAL CONSIDERATIONS

9.1 Study Design/Endpoints

Primary endpoints:

- Safety of commercial CAR19 therapy in PLWH, as assessed by the occurrence of therapy-related toxicities including the ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells, (14) as well as other therapy-related toxicities using the CTCAE v5.0 version
- Efficacy of commercial CAR19 therapy in PLWH, as assessed by the complete response rate at 3 months using the CIBMTR Disease-Specific Manuals for response assessment (https://www.cibmtr.org/manuals/fim/1/en/topic/none)

Secondary endpoints:

- Lymphoma-specific outcomes:
  - Overall response rate and CR rate at 3- and 6-months post CAR19 therapy
  - 3-, 6- and 12-months progression-free and overall survival: The event of interest is defined as per CIBMTR criteria as outlined in Section 8.0.
  - Duration of response: The duration of response will be calculated based on date of first response and progression/death/date of last follow-up (whichever occurs first).
- Treatment, HIV and lymphoma -specific clinical characteristics:
  - CAR T product characteristics, including CAR19 product, time duration from date of leukapheresis to date of cell infusion; cell dose.
  - HIV- and lymphoma-specific participant characteristics, including CD4 count at date of leukapheresis; viral load; ART regimen; prior lymphoma/leukemia therapy; B-cell malignancy subtype; lymphodepleting regimen, as per Table 1.
  - Platelet and neutrophil recovery
  - Non-relapse mortality as defined in Section 8.0.
- Impact of CAR19 therapy on HIV disease:
  - CD4 count and HIV viral load at 3, 6- and 12-months post CART cell infusion.

Exploratory endpoints:

- Association of participant, disease-specific (HIV and lymphoid malignancy) and treatment-specific factors with therapy-related toxicities, CR rate, PFS and OS.

9.2 Sample Size/Accrual Rate

The sample size estimates are not computed to detect a clinically meaningful effect size for a fixed type I/II error rates and are based on logistical reasons. This is an observational cohort and we aim at enrolling 10-30 participants (approximately 2 participants/month). The following Table 3 provides a range of plausible values (95% confidence interval) corresponding to different number of participants that may end up in the final cohort. The estimates are based on sample/observed "Grade 3 or higher CRS and/or immune-effector cell associated neurotoxicity (ICANS)" rate of 30% and are computed using Clopper-

Pearson exact method. Assuming the expected CR rate is also 30%, the range of plausible values (95% confidence intervals) also holds for efficacy estimates. The estimates for ICANS, CRS, and CR rate are based on results of published prospective trials of CAR19 in immunocompetent patients (ZUMA-1 and JULIET).(2,11)

Table 3: Estimated 95% confidence intervals for G3 or higher CRS or ICANS based on number of enrolled participants

Number of Participants	95% CI
10	7%-65%
20	12%-54%
30	15%-49%

9.3 Statistical Analysis

This is an exploratory study. The statistical analysis will be primarily descriptive. Descriptive statistics will be used to summarize the participants characteristics as follows: for categorical and ordinal variables, frequencies and percentages will be calculated; for continuous variables, the mean (standard deviation), or median (interquartile range) will be reported. The distribution of time-to-event endpoints (overall survival, progression free survival, duration of response) will be presented using a Kaplan-Meier plot.

9.4 Analysis of Primary Endpoints

The incidence of toxicities related to CAR19 therapy will be reported as overall as well as separately by a) CTCAE criteria; b) ASTCT consensus grading for cytokine release syndrome (CRS); and c) ASTCT consensus grading for neurologic toxicity associated with immune effector cells (ICANS). A two-sided 95% confidence interval will be reported together with the toxicity rates. The complete response rate will be estimated as the proportion of participants who achieve complete response out of those who are enrolled in the study. A two-sided 95% confidence interval will also be reported together with the complete response rate.

9.5 Analysis of Secondary Endpoints

The CD4 count on date of leukapheresis; viral load; and ART regimen will be summarized using descriptive statistics. The distribution of prior lymphoma/leukemia therapy; B-cell malignancy subtype, lymphodepleting regimen; and CAR T product used will be presented as frequency (percentage). The overall response rate and CR rate at 3 months as 6 months will be summarized separately as frequency (percentage). The estimates of overall, and progression-free survival at 3-,6-, and 12-months will be obtained using Kaplan-Meier plot. The impact of Impact on HIV disease and immune reconstitution will be assessed by evaluating change in CD4 counts and viral load from baseline to subsequent time-points (3, 6, and 12 months), using global Friedman test followed by pairwise signed rank test (if findings from Friedman's test were determined to be statistically significant).

9.6 Analysis of Exploratory Endpoints

The association between categorical variables (participant specific and disease specific) and time-to-event endpoints (OS, PFS) will be tested for statistical significance using log-rank test. The association between continuous variable and time-to-event endpoints (OS, PFS) will be tested for statistical significance using Cox model. The association between categorical variables (participant and disease specific) and complete response status will be tested for statistical significance using either chi-square test or exact test. The association between continuous variables (participant and disease specific) and complete response status will be tested for statistical significance using rank sum test. A two-sided p-value of 0.05 will be used to determine statistical significance. The findings however must be interpreted cautiously (given the exploratory nature of this study).

10.0 ROLE OF DATA MANAGEMENT AND DATA REPORTING

10.1 CRF Instructions

Access to the internet data entry system for this study and instructions for recording of study data on eCRFs will be provided by the CIBMTR (see https://www.cibmtr.org/manuals/fim?v=1&l=en for forms instructions manual). Participating institutions are responsible for submitting data and/or data forms in accordance with the CIBMTR's forms instructions manual and timelines.

10.2 Data Quality

As this is an IRB-exempt, observational cohort study involving secondary data analysis from an externally-managed database, the AMC's responsibility for monitoring the trial is limited to assuring compliance with group policies for trial progress and the security/integrity of the de-identified dataset transferred to the AMC by the CIBMTR. As such, the AMC will comply with the applicable provisions of the AMC Data and Safety Monitoring Plan, provided at Appendix I. This role extends from protocol development to generation of the final study database.

10.3 Data Monitoring

Data for this study will be submitted via the Data Mapping Utility (DMU). Cumulative patient demographic data will be submitted to CTEP electronically via the DMU. Instructions for setting up and submitting data via DMU are available on the CTEP Website: (https://ctep.cancer.gov/protocolDevelopment/dmu.htm).

11.0 ETHICAL AND REGULATORY CONSIDERATIONS

11.1 IRB Exemption Justification

The AMC has assessed that this research protocol qualifies as exempt research under 45 CFR 46.104(d)(4)(ii). The trial will involve secondary research for which informed consent is not required, as this involves the use of deidentified health information in the CIBMTR's Cellular Therapy Registry. Participant information in this database is collected from patients who provide informed consent to include their data in the Cellular Therapy Registry. The AMC's use of this information for this protocol will involve the use of health information that is recorded by the reporting clinical centers in such a manner that the identity of the human subjects cannot readily be ascertained directly or through identifiers linked to the subjects (CIBMTR Case ID used). The CIBMTR and the clinical site contributing data to the CIBMTR will not contact the subjects, and the CIBMTR will not re-identify subjects for the required analysis. All data will be collected through the CIBMTR's Cellular Therapy Registry, and provided to the AMC in a de-identified, secure manner.

11.2 Changes to the Protocol

Any change or addition to this protocol requires a written protocol amendment that must be approved by CTEP before implementation.

11.3 Women and Minorities

This study is being conducted by the NCI-sponsored AIDS Malignancy Consortium (AMC). As part of their contractual obligations, each participating site within the AMC, and the AMC/its collaborators are required to assure that the participation of women and minority participants reflects the percentage representation of these populations in their geographic region and, for the AMC, the United States as a whole. As such, it is expected that the representation of participants on this trial will reflect the constitution of the respective populations.

Table 4: Accrual Targets

DOMESTIC PLANNED SCREENING ENROLLMENT REPORT					
Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	0	0	0	0	0
Asian	0	1	0	0	1
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	3	4	2	3	12

DOMESTIC PLANNED SCREENING ENROLLMENT REPORT					
White	4	4	2	3	13
More Than One Race	1	1	1	1	4
Total	8	10	5	7	30

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	0	0	0	0
Asian	0	1	0	0	1
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	3	4	2	3	12
White	4	4	2	3	13
More Than One Race	1	1	1	1	4
Total	8	10	5	7	30

Enter actual estimates, whole numbers only (percentages, fractions, or decimals are not acceptable).

The totals provided for each Ethnic/gender or Ethnic/total combination must match those given for each Race/gender or Race/total combination (i.e., A1 must match A2, B1 must match B2, and C1 must match C2).

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