CLINICAL STUDY PROTOCOL

	Safety and Feasibility Study of Chimeric Antigen Receptor (CAR) T Cell Therapy with YESCARTA in the Outpatient Setting
Concept Summary	Safely transitioning YESCARTA® (axicabtagene ciloleucel) treatment to the outpatient setting
Investigational Site	Vanderbilt-Ingram Cancer Center
Support	Kite Pharma, Inc.
Clinicaltrials.gov number	NCT05108805
Sponsor-Investigator	Olalekan O. Oluwole, MD, MPH
Original Protocol Date	17 June 2021
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Protocol v4.1	11 November 2022
Protocol v4.2	06 January 2023
Protocol v4.3	05 September 2023

Oluwole YESCARTA in the outpatient setting.
05SEP23

PROTOCOL SYNOPSIS

Title	Safely transitioning YESCARTA® (axicabtagene ciloleucel) treatment to the outpatient setting.
Indication	Exploring the feasibility of outpatient treatment with YESCARTA.
Stucdy Design	This study is an open label non-randomized treatment with YESCARTA in the outpatient setting. The purpose is to demonstrate that YESCARTA can be safely administered in the outpatient setting if we closely monitor subjects with physical exams, wearable devices, and telemedicine visits and only admit those who meet specified criteria Enrollment and apheresis: Eligible subjects are enrolled and apheresed per YESCARTA protocol Day -5 to -3: Pre-lymphodepleting Period. Subjects and family are trained to do vital signs, use wearable devices, and operate equipment suitable for telemedicine. Patients who remain eligible for outpatient therapy will proceed to receive lymphodepleting chemotherapy day -5 to -3 Day 0: Subjects report to the clinic in the morning of day 0 for physical exam and laboratory tests. The Immune Effector Cell-Associated Encephalopathy (ICE) score will be calculated. YESCARTA is infused in the outpatient clinic and subject monitored for 2 hours post-infusion before they are discharged to the apartment. A telemedicine evaluation is done at 16:30 PM and 22:00 ± 1 hour which includes a review of systems, physical exam including neurological assessment (ICE score), and vital signs. Subject will awake in AM, family will obtain vital signs at 06:30 ± 1 hour, and place a call to the covering NP to report the vital signs prior to presenting to the outpatient clinic at 08:00 AM. Day 1 – Day 14: 1. 08:00 AM: Subject reports to the outpatient clinic at 8am daily including weekends. Vital signs log reviewed by NP and equipment checked. Laboratory tests are ordered per protocol. Physical exam by NP and attending physician both of whom review all available data including the ICE score. Subject discharged back to the apartment by 10:00 AM or shortly after if no criteria for hospitalization are met. 2. 12:00: Subject and family take their blood pressure and pulse oximeter using the device provided. They will call NP line if they

	become aware of abnormal vital signs or a change in patient's status. 3. 16:30 and 22:00 ± 1 hour: Telemedicine visit with night NP. Telemedicine details: Subject and NP will activate the telemedicine App in their electronic device. Family will obtain vital signs (BP, HR, RR, SPO2) and provide NP with the information. NP will also review the previous vital signs at 12:00 and/or 16:30. Review of system questions are asked, and the answers given by subject recorded. Neurological assessment done, and ICE score calculated. Criteria for admission to the hospital: 1. Fever ≥102 F or higher, or fever 100.4 to < 102 with a change in status (e.g. hypotension, altered mental status or other sign of end organ dysfunction). Fever < 102 alone without other symptom can be closely monitored in the outpatient setting per written institution guidelines. 2. Hemodynamic instability: (any of the following) Hypotension that requires IV fluids, MAP < 20% of baseline or SBP < 90 mmHg or HR > 130/min 3. Sustained hypoxia with SPO2 < 90% 4. Abnormal neurological function (grade 1 or higher ICANS) based on the ICE score 5. Other criteria at the discretion of the covering physician. For study requirements, refer to **Section 7** and the schedule of assessments (SOAs) in **Section 8** for details. A study schema is provided in Figure 1 (**Section 6.3.4.2**).
Study Objectives	The primary objective is to explore the feasibility of treating subjects with YESCARTA in the outpatient setting and determine the number of subjects who remain outpatient through 72 hours, 7, 14, and 30 days. Secondary Objectives are to identify risk factors that preclude outpatient administration, obtain clinical data that will inform the development of guidelines by which YESCARTA treatment can be done in safely in the outpatient setting, and assess the impact of telemedicine and close monitoring on specific outcomes including CRS and ICANS in subjects

	treated with YESCARTA in the outpatient setting. Data from wearable device are collected for research only.
Study Hypothesis	No formal statistical hypothesis will be tested. All analyses will be descriptive.
Study Endpoints	1. Number of subjects that remain an outpatient at 3, 7 and 30 days after YESCARTA infusion. 2. Time to requirement for inpatient hospitalization after YESCARTA infusion. 3. Incidence/grade of adverse events, CRS and ICANS 4. Incidence of steroid and/or tocilizumab administration 5. YESCARTA treatment response rate.
Sample Size	Twenty subjects will receive YESCARTA treatment
Study Eligibility	Refer to **Section 5** for a complete and detailed list of inclusion and exclusion criteria.
Treatment	1. Conditioning chemotherapy regimen consisting of cyclophosphamide 500 mg/m^2/day and fludarabine 30 mg/m2/day will be administered for 3 days prior to YESCARTA infusion. Refer to **Section 6** for chemotherapy treatment details. 2. YESCARTA treatment consists of a single infusion of chimeric antigen receptor (CAR) transduced autologous T cells administered intravenously at a target dose of 2 x 10^6 anti-CD19 CAR T cells/kg. Refer to **Section 6** and **Section 7** for treatment details. Adjunct to treatment: oral dexamethasone 10 mg once daily for 3 days, starting prior to YESCARTA infusion on Day 0
Safety Review and Data Monitoring	A safety review team (SRT) will be established that consists of PI, sub-I and study sponsor representative. The SRT will review safety data after 10 subjects are treated and make recommendations regarding further study conduct based on the overall safety profile of YESCARTA.
Statistical Considerations	The statistical reporting of the safety and efficacy endpoints will be entirely descriptive; no formal statistical testing will be performed. The subject incidence rates of AEs and clinically significant changes in safety lab values will be summarized. See Appendix E for detailed statistical considerations.

STUDY GLOSSARY

AE	Adverse event
ALL	Acute lymphoblastic leukemia
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count

ASCT	Autologous stem cell transplant
AST	Aspartate aminotransferase
AUC	Area under the curve
BBB	Blood brain barrier
BP	Blood Pressure
BUN	Blood urea nitrogen
CAR	Chimeric antigen receptor
CBC	Complete blood count
CLL	Chronic lymphocytic leukemia
CMP	Complete Metabolic panel
CMV	Cytomegalovirus
CNS	Central nervous system
CPF	Cell processing facility
CR	Complete response
CRF	Case report form
CRP	C-reactive protein
CRS	Cytokine release syndrome
CSF	Cerebrospinal fluid
CTCAE	Common Terminology Criteria for Adverse Events
DLBCL	Diffuse large B-cell lymphoma
DLT	Dose-limiting toxicity
DOR	Duration of response
DSMB	Data Safety Monitoring Board
eACTTM	Engineered autologous cell therapy
EBV	Epstein-Barr virus
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
EQ-5D	European Quality of Life-5 Dimensions
FAS	Full analysis set
FL	Follicular lymphoma
GCP	Good Clinical Practice
GOT	Glutamic-oxaloacetic transaminase
GPT	Glutamic-pyruvic transaminase
HCT	Hematopoietic stem cell transplant
HGBCL	High grade B-cell lymphoma
HIV	Human immunodeficiency virus
HR	Heart Rate
HLH	Hemophagocytic lymphohistiocytosis
HSCT	Hematopoietic stem cell transplantation
IB	Investigator’s Brochure
ICE	Immune Effector Cell-Associated Encephalopathy
ICANS	Immune effector cell-associated neurotoxicity syndrome
IC	Investigator’s choice
ICF	Informed consent form
ICH	International Conference on Harmonization
ICU	Intensive care unit
ID	Identification

IDSA	Infectious Diseases Society of America
IEC	Independent Ethics Committee
IFN	Interferon
IHC	Immunohistochemistry
IL	Interleukin
ImiD	Immunomodulatory drug
IP	Investigational product
IPM	Investigational Product Manual
IRB	Institutional Review Board
IRT	Interactive response technology
IUD	Intrauterine device
IV	Intravenous
LDH	Long-term follow-up
LTFU	Left ventricular ejection fraction
LVEF	Lactate Dehydrogenase
mAb	Monoclonal antibody
MASCC	Multinational Association of Supportive Care of Cancer
MDS	Myelodysplastic syndrome
mITT	Modified intent-to-treat
MRI	Magnetic resonance imaging
NCI	National Cancer Institute
NHL	Non-Hodgkin lymphoma
NK	Natural killer
NPT	Nasopharyngeal-throat
ORR	Objective response rate
OS	Overall survival
PBMC	Peripheral blood mononuclear cell
PCR	Polymerase chain reaction
PD	Progressive disease
PET-CT	Positron emission tomography-computed tomography
PFS	Progression-free survival
PK	Pharmacokinetics
PO	Taken orally
PR	Partial response
qd	Every day
qPCR	Quantitative polymerase chain reaction
RCR	Replication-competent retrovirus
REMS	Risk Evaluation and Mitigation Strategy
SAE	Serious adverse event
scFv	Single-chain variable fragment
SCT	Stem cell transplant
SD	Stable disease
SmPC	Summary of product characteristics
SOA	Schedule of assessment
SRT	Safety review team
SSAP	Supplementary statistical analysis plan
TEAE	Treatment-emergent adverse event
TLS	Tumor lysis syndrome

TNF	Tumor necrosis factor
UA	Urinalysis
ULN	Upper limit of normal
USPI	United States Prescribing Information
UTI	Urinary tract infection
WBC	White blood cell

1. OBJECTIVES

1.1. Primary Objectives

- To explore the feasibility of treating subjects with YESCARTA in the outpatient setting and guide the development of a subsequent, larger study that will determine the tolerability and safety profile of YESCARTA in the outpatient setting.
- To determine the time to specific interventions post infusion and the number of subjects who remain outpatient through 72 hours, 7, 14, and 30 days.

1.2. Secondary Objectives

- Identify risk factors that preclude outpatient administration, and to obtain clinical data that will guide the development of guidelines by which YESCARTA treatment in the outpatient setting can be done safely**.**
- Assess the impact of close monitoring with telemedicine and close monitoring on specific outcomes including CRS and ICANS in subjects treated with YESCARTA in the outpatient setting.
- Cumulative steroid exposure within 28 days post YESCARTA infusion.
- To calculate the estimated cost of YESCARTA administered in the outpatient setting.

1.3. Exploratory Objectives

- Time from YESCARTA infusion to the following: fever, fever with neutropenia, fever without neutropenia.
- Time from fever to Tocilizumab, fever to ICU admission, fever to low BP, fever to IV Fluid, fever to vasopressor, fever to onset to arrhythmias and fever to hospitalization.
- Calculate modified Neutropenic Fever Symptom Burden (NFSB) score for days 1-3 for each subject. Appendix D
- Obtain subject reported outcomes measured by Subject-Reported Outcomes Measurement Information System (PROMIS; Appendix F) [16, 17]

- Feasibility of using wearable devices to monitor vital signs in the outpatient setting. Data collected are for research only.

2. DISEASE BACKGROUND AND RATIONALE

2.1. Background

Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of large B-cell lymphoma with approximately 22,000 new diagnoses each year in the United States. Cytotoxic chemotherapy is curative in 40 to 60% of the subjects. However, subjects with relapsed or chemotherapy refractory DLBCL have a particularly dire prognosis.[1]

2.2. Yescarta

Axicabtagene ciloleucel (YESCARTA®) is approved by the US Food and Drug Administration (FDA) based on ZUMA-1 data with objective response rate was 82%, the complete response rate was 54% and the overall rate of survival at 18 months was 52%.[2] The current standard practice is to only administer YESCARTA as inpatient and monitor for at least 7 to 10 days for side effects including cytokine release syndrome (CRS) and Immune effector cell-associated neurotoxicity syndrome (ICANS).

To date, YESCARTA is the best product in its class with the highest objective response rate and longest duration of response of any CAR T therapy. However, the prolonged hospital stays, and high cost have limited its use[3]. Furthermore, outpatient therapies in general are viewed more favorably due to less resource utilization and it is conceivable that many centers may opt for a competing product like tisagenlecleucel or lisocabtagene maraleucel because of the perceived notion that they might be more amenable to being used in the outpatient setting.[4, 5]

2.3. Rationale for Outpatient Therapy

Whereas YESCARTA treatment in the inpatient setting is feasible and the ZUMA-1 trial reported grade 3 or higher CRS and ICANS in 13% and 28% of subjects respectively, the impact of such a therapy in the outpatient setting and the safety profile of outpatient therapy remains largely unexplored.[6, 7]

Zuma-1 data and our institution data suggest that fever is the earliest sign of CRS in the recipients of YESCARTA. In our database search of 20 subjects treated with YESCARTA at Vanderbilt, nine (45%) did not develop fever until after 72 hours from the time of YESCARTA infusion suggesting that there is the possibility that subjects could have been managed at least in part in the outpatient setting which will lead to a reduction in the total number of days spent in the hospital. A similar system was used to determine who could undergo HCT in the outpatient setting. That study showed a reduction in hospital length of stay and significant cost savings.[8]

At Vanderbilt, 70% of all allogeneic HCT are done in the out-patient setting. Most matched related and unrelated transplants are done in the outpatient setting with brief period of hospitalization to administer thymoglobulin, while we electively admit haploidentical transplant subjects till completion of high dose Cytoxan. In our single institution quality review for 2018, we performed 18 matched related transplants in the outpatient setting. Eight of the 18 subjects ended up being admitted and incurred a total of 42 hospital days at an average of 2.3 days per subject for the whole cohort. In that same year, we performed 4 haploidentical transplants in the inpatient setting and incurred a total of 24 days of hospitalization which is an average of 6 days per subject (unpublished data). While cost comparisons are not as easy to do, we can postulate that the reduction in hospital length of stay translates into fewer interruptions in subject's life, reduced exposure to hospital acquired infections, improved quality of life and healthcare savings. Currently, no risk model has been developed with the ability to carefully identify those who can safely be treated in the outpatient setting with any CAR T product and the benefit of using specific clinical parameters to determine who will benefit from early escalation of care to the inpatient setting is also unknown.

2.4. Rationale for Selecting Vanderbilt Transplant and Cellular Therapy Program

In 2005, Vanderbilt invested in the design of our outpatient transplant unit (OTU) where our HCT program is nested and with which we transitioned all hematopoietic cell transplants (autologous and allogeneic) to the outpatient setting. These subjects are only admitted if a clinical need arises which cannot be managed in the outpatient setting. Our internal quality data suggests that this transition has been cost-effective through reduction in number of hospital days per subject without negatively impacting transplant outcomes. The outpatient transplant unit is complete with a series of dedicated infusion bay areas where subjects can receive immediate attention from nurses, mid-level providers and attending physicians. Subjects are seen daily and as needed. The unit is open 8:00 AM – 5:00 PM, seven days a week. We also have a dedicated telemedicine service for cellular therapy subjects which can be utilized for any urgent issues or routine clinical monitoring when subject is not in the clinic. Our quality metrics, subject outcomes, and subject satisfaction compare favorably to the other transplant centers which primarily manage the complex subjects in the inpatient units during early peri-transplant period. We transplant between 300 and 400 subjects annually and many of the subjects remain in the outpatient setting throughout the transplant process. Subjects are housed within 30 miles from the hospital in specified lodging facilities, and we have a tested system of stat bed(s) with which we can initiate specific therapy within 30 – 60 minutes at any time day or night. For the proposed pilot study, subjects will be housed in select apartments that allow for them to reach the hospital within 15 minutes. Our telemedicine service line has outcomes comparable to face to face clinic visits and has been successfully integrated into our HCT workflow (unpublished data).

3. STUDY DESIGN

3.1. General Study Design

This is an open label non-randomized feasibility study primarily designed to evaluate the safety and effectiveness of close monitoring and telemedicine in the treatment of subjects with YESCARTA in the outpatient setting.

Study candidates are adults with recurrent large B-cell lymphoma who are refractory to prior chemotherapy or have had ASCT. They must have at least 1 measurable lesion and meet multiple organ function criteria.

3.2. Rationale for Close Monitoring in the Outpatient Setting

Subjects who are hospitalized get to have vital signs up to six times each day and physical exams and/or close monitoring by physician and 1 or more nurses which allows ample opportunities to pick up on and act on changes to the subject's status. This is in stark contrast to the outpatient with whom there may be long gaps when there is no contact with any health personnel. The desire to bridge this gap and ensure safety in the outpatient setting is the rationale behind asking that outpatients be seen and examined twice each day.

3.3. Participating Site and Number of Subjects

Vanderbilt University Medical Center.

3.4. Number of Subjects

Participants in this study will be referred to as "subjects." It is anticipated that 20 will be enrolled into this study.

3.5. Study Duration

3.5.1. Study Duration for Individual Subjects

The duration of the study for individual subjects will vary. For a subject who completes the entire protocol from the date of informed consent through the completion of the long-term follow-up (LTFU) period, the duration of the study is 12 months. However, an individual subject's study duration will vary depending on the subject's screening requirements, response to treatment, and survival.

3.5.2. Completion of Study

Completion of the study is defined as the time at which the last subject completes the LTFU period visit, is considered lost to follow-up, withdraws consent, or dies.

4. ENROLLMENT PROCEDURES

All patients MUST be registered prior to the start of study procedures such as tissue acquisition. Registration can only be conducted during the business hours of 8AM – 5PM Central Time, Monday through Friday.

1) If a subject ID number is required prior to patient enrollment (i.e. at screening due to sample collection requirement), the site must submit the following documents with their email notification to the Study Coordinator:

    - Copy of the patient's signed and dated Informed Consent including documentation of the consent process.
    - HIPAA authorization form (if separate from the main consent form).
    - VICC Patient Enrollment Form.

    The Study Coordinator will then provide a subject ID number via email.

2) Email the following documents to the VICC CTO Registrar Office for eligibility review and (viccctsrregistraroffice@vumc.org):

    - Copy of the patient's signed and dated Informed Consent, including documentation of the consent process.
    - HIPAA authorization form (if separate from the main consent form).
    - VICC Patient Enrollment Form.
    - Eligibility supporting documents such as pathology reports, laboratory tests, etc. *or* EMR access. Note: all source documents should be de-identified and screening/subject ID number added prior to sending.
    - Signed and completed Eligibility Checklist. **To be eligible for registration to the study, the participant must meet each inclusion and exclusion criterion listed in the eligibility checklist.**

Note: The VICC CTO Registrar Office requires 3 business days to review all documents and confirm eligibility. Registrations will only be accepted with prior notice and discussion with the Lead Institution. Please email the clinical tr[redacted] vumc.org.

Upon satisfactory review of eligibility documents submitted, the Study Coordinator will approve enrollment and issue a subject ID number if one was not issued at screening. Once registration/enrollment confirmation from the Study Coordinator is received, proceed with protocol procedures.

Please contact the assigned Study Contact with any questions regarding this process. You can also reach out to your assigned CRA once the study is activated.

The Study Coordinator will assign Subject ID numbers to all patients whose eligibility has been confirmed. Only patients deemed eligible will be registered to the study. Sequence/study ID numbers will not be re-used if a patient screen fails. Following registration, eligible participants should begin the study consistent with the protocol no later than 28 days after registration/enrollment by the VICC Coordinating Center.

Subjects who are unable to complete or meet the eligibility criteria will be permitted to rescreen one time. If rescreening occurs within 28 days of the signing of the original informed consent, only the procedure(s)/assessment(s) that did not originally meet the eligibility criteria needs to be repeated; all other initial screening procedures/assessments do not need to be repeated. If rescreening occurs, or leukapheresis is delayed, more than 28 days from the signing of the original informed consent, subjects must be reconsented and repeat all screening procedures/assessments.

If a participant does not begin the study following registration within the allowed time period, the participant's registration on the study will be canceled. The Study Contact will be notified of cancellations as soon as possible. Patients being re-screened will need to consent to repeated procedures. As such, the Coordinating Center will require a new, signed Informed Consent document.

Issues that would cause treatment delays should be discussed with the sponsor-investigator.

As is generally accepted, standard of care procedures performed prior to consent, but within the protocol defined screening window for each assessment, can be used for study purposes. All research-only procedures must be performed after patient consent.

5. SUBJECT ELIGIBILITY

5.1. Inclusion Criteria (before leukapheresis)

1. Age 18 years and above.

2. Histologically proven large B cell lymphoma or transformed follicular lymphoma to DLBCL in relapse/refractory after two lines of therapies which included an anthracycline and CD20-targeted therapy.

   Or

3. Chemotherapy refractory disease evidenced by lack of adequate response to first line therapy. This consists of either progressive disease as best response to first line therapy or stable disease as best response after 4 cycles of appropriate chemotherapy

   Or

4. Refractory after ASCT at any time point

And

5. ECOG performance status 0-2.

6. Adequate hematologic, hepatic, renal and cardiac function evidenced by:

   a. ANC ≥1000/µL
   b. Platelet ≥ 75,000/ µL
   c. T-bilirubin ≤ 1.5 mg/dL
   d. Normal serum creatinine or creatinine clearance ≥ 60 mL/min/1.73 m^2
   e. Cardiac ejection fraction ≥ 50%
   f. Serum alanine aminotransferase/aspartate aminotransferase (ALT/AST) ≤ 5 times upper limit of normal (ULN).

7. At least 1 measurable lesion

8. Baseline oxygen saturation ≥92% on room air.

9. Ability to stay at a distance which allows for subjects to come in and for specific interventions like antibiotics and tocilizumab to be started in 1 hour or less. This is approximately 30 miles of Vanderbilt.

10. A caregiver who can be educated to operate equipment for vital signs monitoring.

11. Caregiver Eligibility

    i. Willingness to serve as a caregiver
    ii. Ability to read, write and operate a phone
    iii. Willingness to be taught to operate electronic device
    iv. Willingness and ability to assist subject to wear electronic device such including patch, blood pressure machine, thermometer
    v. Pass caregiver assessment test

12. Subject and caregiver willing to be taught to operate an iPad or other electronic media for telemedicine, use wearable devices, and pass the caregiver competence test.

5.2. Exclusion Criteria

1. History of malignancy other than nonmelanoma skin cancer or carcinoma in situ (e.g. cervix, bladder, breast) or follicular lymphoma unless disease free for at least 3 years.

2. Known CD19 negative tumor.

3. History of Richter's transformation of CLL.

4. Autologous stem cell transplant with therapeutic intent within 6 weeks of planned YESCARTA infusion.

5. History of allogeneic stem cell transplantation.

6. Prior CAR therapy or other genetically modified T-cell therapy.

7. History of severe, immediate hypersensitivity reaction attributed to aminoglycosides.

8. Presence or suspicion of fungal, bacterial, viral, or other infection that is uncontrolled or requiring IV antimicrobials for management. Simple urinary tract infection (UTI) and uncomplicated bacterial pharyngitis are permitted if responding to active treatment and after consultation with the sponsor's medical monitor.

9. History of human immunodeficiency virus (HIV) infection or acute or chronic hepatitis B or hepatitis C infection. Subjects with history of hepatitis infection must have cleared their infection as determined by standard serological and genetic testing per current Infectious Diseases Society of America (IDSA) guidelines or applicable country guidelines.

10. Presence of any in-dwelling line or drain (e.g., percutaneous nephrostomy tube, in-dwelling Foley catheter, biliary drain, or pleural/peritoneal/pericardial catheter). Dedicated central venous access catheters, such as a Port-a-Cath or Hickman catheter, are permitted.

11. Subjects with detectable cerebrospinal fluid malignant cells, or brain metastases, or with a history of CNS lymphoma or primary CNS lymphoma, cerebrospinal fluid malignant cells or brain metastases. Patients with treated secondary CNS involvement of lymphoma are allowed.

12. History or presence of CNS disorder, such as seizure disorder, cerebrovascular ischemia/hemorrhage, dementia, cerebellar disease, progressive multifocal leukoencephalopathy, or any autoimmune disease with CNS involvement if it impairs ability to complete an effective and reliable neurological assessment.

13. Subjects with cardiac atrial or cardiac ventricular lymphoma involvement.

14. History of myocardial infarction, cardiac angioplasty or stenting, unstable angina, or other clinically significant cardiac disease within 12 months of enrolment.

15. Requirement for urgent therapy due to tumor mass effects (e.g., blood vessel compression, bowel obstruction, or transmural gastric involvement).

16. Primary immunodeficiency.

17. Any medical condition likely to interfere with assessment of safety or efficacy of study treatment.

18. Live vaccine ≤ 6 weeks prior to planned start of conditioning regimen.

19. History of severe immediate hypersensitivity reaction to any of the agents used in this study.

20. Women of child-bearing potential who are pregnant or breastfeeding because of the potentially dangerous effects of the preparative chemotherapy on the fetus or infant. Females who have undergone surgical sterilization or who have been postmenopausal for at least 2 years are not considered to be of childbearing potential.

21. Subjects of both genders who are not willing to practice birth control from the time of consent through 6 months after the completion of conditioning chemotherapy.

22. In the investigator's judgment, the subject is unlikely to complete all protocol-required study visits or procedures, including follow-up visits, or comply with the study requirements for participation.

23. History of autoimmune disease (e.g. Crohn's, rheumatoid arthritis, systemic lupus) resulting in end organ injury or requiring systemic immunosuppression/systemic disease modifying agents within the last 2 years.

24. Must not have received immunomodulating agents including checkpoint inhibitors, BTK inhibitors, and Revlimid within 2 months or 5 half-lives whichever is shorter.

6. PROTOCOL TREATMENT

6.1. Treatment Terminology

Bridging therapy refers to treatment used to control a subject's disease prior to lymphodepleting chemotherapy.

Telemedicine refers to the use of specified video and audio software with the purpose to evaluate the status of the subject.

6.2. Study Treatment

6.2.1. Pre-lymphodepleting period

6.2.1.1. Leukapheresis

Leukapheresis refers to the procedure for collecting peripheral blood mononuclear cells (PBMCs) that are used to manufacture the subject-specific YESCARTA treatment. Subjects will undergo leukapheresis to obtain T cells for the manufacturing of YESCARTA. Leukapheresed cells obtained will be shipped to the supporter's manufacturing facility as described in the Investigational Product Manual (IPM).

6.2.1.2. Bridging Therapy

Bridging therapy will be obtained by the investigative site unless otherwise noted.

Table 1. Bridging Therapy

Type	Therapy Regimen	Timing and washout
Corticosteroid	Dexamethasone at a dose of 20 mg to 40 mg or equivalent, either PO or IV daily for 1 to 4 days.	May be administered after apheresis/enrollment and must be completed at least 5 days prior to the start of lymphodepleting chemotherapy.
HDMP + Rituximab	1 gram/m2 of high dose methylprednisolone (HDMP) for 3 days in combination with rituximab at 375 mg/m2 weekly for 3 weeks.	May be administered after enrollment and completed at least 7 days prior to the start of lymphodepleting chemotherapy.

6.2.1.3. Subject and caregiver training

Subject and caregiver education procedure included a series of training sessions designed to equip them with necessary skills to take reliable and reproducible vital signs. It also includes training to operate a tablet, laptop or smartphone application that will be used for the telemedicine encounter. This process ends with a caregiver certification process during which the nurse formally tests and verifies that family can measure vital signs reliably. A dry run of the telemedicine

on a set date will also be done and be repeated as needed till all aspects are completed without error. Upon successful completion of caregiver education and dry run, the subject will proceed to get lymphodepletion chemotherapy as from Day -5.

6.2.1.4. Verification of Eligibility to proceed to Lymphodepletion Therapy

Preparation for lymphodepleting chemotherapy is done between Day -9 and Day -6 to ensure that only those who remain eligible per criteria below will continue the treatment pathway for outpatient YESCARTA. Ineligible patients will receive YESCARTA per standard of care. This second screening does not require another consent.

1. ANC ≥1k/µL,
2. Platelet ≥ 75k/ µL,
3. T-bili ≤ 1.5 mg/dL,
4. Creatinine clearance ≥ 60 mL/min/1.73 m^2, and
5. Oxygen saturation ≥92% on room air.

6.2.2. Lymphodepletion Chemotherapy

Lymphodepleting chemotherapy refers to fludarabine and cyclophosphamide used for lymphodepletion before administration of YESCARTA. Lymphodepleting chemotherapy will be supplied by the investigative site unless otherwise noted. Refer to the current product label for guidance on packaging, storage, preparation, administration, and toxicity management associated with the administration of chemotherapy agents.

6.2.2.1. Fludarabine

Fludarabine phosphate is a synthetic purine nucleoside that differs from physiologic nucleosides in that the sugar moiety is arabinose instead of ribose or deoxyribose. Fludarabine is a purine antagonist antimetabolite. Refer to the most recent version of the package insert for specific details surrounding the administration of fludarabine.

6.2.2.2. Cyclophosphamide

Cyclophosphamide is a nitrogen mustard-derivative that acts as an alkylating agent following conversion to active metabolites in the liver and has potent immunosuppressive activity. The serum half-life after IV administration ranges from 3 to 12 hours; the drug and/or its metabolites can be detected in the serum for up to 72 hours after administration. Refer to the current version of the

package insert for specific details associated with the administration of cyclophosphamide.

6.2.2.3. Mesna

Mesna is a detoxifying agent used to inhibit the hemorrhagic cystitis induced by chemotherapy. The active ingredient in mesna is a synthetic sulfhydryl compound designated as sodium-2- mercaptoethane sulfonate with a molecular formula of C2H5NaO3S2. Mesna should be administered per institutional guidelines. Refer to the current version of the package insert for specific details surrounding the administration of mesna.

6.2.3. YESCARTA

YESCARTA is supplied cryopreserved in cryostorage bags. The product in the bag is slightly cloudy and cream to yellow color. The cryostorage bag containing YESCARTA arrives frozen in a liquid nitrogen dry shipper. The bag must be stored in a vapor phase of liquid nitrogen and remain frozen until the subject is ready for treatment to assure that viable live autologous cells are administered to the subject. Several inactive ingredients are added to the product to assure viability and stability of the live cells through the freezing, thawing, and infusion process.

YESCARTA is a subject-specific product. The product is labelled per sponsor protocol. Upon receipt, verification that the product and subject-specific labels match the subject's information is essential. Do not infuse the product if the information on the subject specific label does not match the intended subject. The volume of YESCARTA infused, the thaw start/stop time, and YESCARTA administration start/stop time will all be noted in the subject medical record. The product must not be thawed until the subject is ready for the infusion. Refer to the IPM for details and instructions on storage, thawing, and administration of YESCARTA. There have been no instances of accidental overdose of subjects in this program to date. In case of accidental overdose, treatment should be supportive. Corticosteroid therapy may be considered if any dose is associated with severe toxicity. Toxicity management guidelines are found in the current product IB version 10.0 (e.g. Section 6.5) and should be consulted. If any problems related to the use of YESCARTA or any products that support the management of YESCARTA (e.g., cryostorage bags, subject ID labels) are identified, research staff should report the problem per the instructions in the IPM.

6.2.4. Concomitant Therapy

Concomitant therapy refers to treatment that subjects receive during the conduct of the study. During the course of the study, investigators may prescribe any concomitant therapies deemed necessary to provide adequate supportive care except those medications listed in **Section 6.2.5**. All concomitant therapies, including medications, intubation, dialysis, oxygen, and blood products, will be recorded.

All concurrent therapies, including medications, intubation, dialysis, oxygen, and blood products, will be recorded from the date of the informed consent through day 30 after completing treatment with YESCARTA or until disease progression, whichever occurs first.

For subjects who are enrolled but not dosed with YESCARTA, concurrent therapies will only be recorded from the date of the informed consent through 30 days after the last study specific procedure (e.g., leukapheresis, lymphodepleting chemotherapy). For subjects who are not enrolled (e.g., screen failure or not leukapheresed), only concurrent therapies related to any serious adverse event(s) will be recorded.

6.2.5. Excluded Medications

Corticosteroid therapy at a pharmacologic dose (≥ 5 mg/day of prednisone or equivalent doses of other corticosteroids) and other immunosuppressive drugs must be avoided for 7 days prior to leukapheresis, and 5 days prior to YESCARTA administration. Corticosteroids and other immunosuppressive drugs should also be avoided for 3 months after YESCARTA administration, unless used to manage YESCARTA related toxicities (refer to the investigator brochure version 10.0 and YESCARTA package insert). Other medications that might interfere with the evaluation of the investigational product, such as non-steroidal anti-inflammatory agents should also be avoided for the same time period unless medically necessary.

Treatment for lymphoma such as chemotherapy, immunotherapy, targeted agents, radiation, and high dose corticosteroid, other than defined/allowed in this protocol, and other investigational agents are prohibited, except as needed for treatment of disease progression after the YESCARTA infusion.

6.3. Study Treatment Schedule

6.3.1. Leukapheresis (Within Approximately 5 Days of Eligibility Confirmation)

Subjects will undergo leukapheresis (12-15 liter apheresis with a goal to target approximately 5-10 x 10^9 mononuclear cells) for the manufacturing of YESCARTA. Leukapheresed cells are shipped to the cell processing facility (CPF) overnight as described in the Investigational Product Manual. Once a subject commences leukapheresis, the subject is considered enrolled in the study.

6.3.2. Chemotherapy General Instructions

Subjects will initiate lymphodepleting chemotherapy with cyclophosphamide and fludarabine beginning on Day -5.

6.3.3. YESCARTA General Instructions

The following medications should be administered approximately 1 hour prior to YESCARTA infusion.

- Acetaminophen 500 to 1000 mg PO
- Diphenhydramine (12.5 to 25 mg IV or 25 mg PO)
- Dexamethasone 10mg PO, 1 hour before Yescarta infusion and on days 1 and 2

Central venous access, such as a port or a peripherally inserted central catheter, is required for the administration of YESCARTA. Catheter care, per institutional guidelines, should be

followed. Materials and instructions for the thawing, timing, and administering of YESCARTA are outlined in the Investigational Product Manual which must be reviewed prior to administration of YESCARTA.

6.3.4. Post Infusion Monitoring

Figure 1: Subject's daily monitoring workflow during first 14 days after YESCARTA infusion.

6.3.4.1. Day Zero

Subject will report to the clinic in the morning for evaluation including physical exam and laboratory tests. Baseline BP, HR, RR, SPO2, laboratory tests (CBC, CMP, LDH, CRP, ferritin, magnesium, uric acid, phosphorus, and fibrinogen) will be obtained. Baseline neurological exam details are verified. The Immune Effector Cell-Associated Encephalopathy (ICE) score will be calculated. [9]

YESCARTA will be infused in the outpatient clinic and subject monitored for 2 hours post-infusion before they are discharged to the apartment. Telemedicine visit by NP is done at 16:30 PM and 22:00 ± 1 hour. This includes a review of systems, physical exam including neurological assessment (ICE score), and vital signs Subject will awake in am, obtain vital signs at 06:30 ± 1 hourand call in with the vital signs prior to presenting to the outpatient clinic at 8am.

6.3.4.2. Day 1 – Day 14: (Figure 1)

1. 6:00 AM:
   Subject and family take their vital signs (BP, HR, RR, SPO2) and record in the logbook. Call NP line if pre-specified criteria for hospital admission are met.
2. 8:00 AM:
   Subject will report to the outpatient clinic at 8am daily including weekends. Vital signs log reviewed by nurse practitioner (NP) and equipment checked for functionality. Laboratory tests including correlatives are ordered per protocol. Physical exam by NP and attending physician both of whom will review all available data including the ICE score. Subject discharged back to the apartment by 10:00 AM or shortly after if no criteria for hospitalization are met.
3. 12:00 noon:
   Subject and family take their vital signs (BP, HR, RR, SPO2) and record in the logbook. Call NP line if pre-specified criteria for hospital admission are met.
4. 16:30 and 22:00 ± 1 hour:
   Telemedicine visit. Vitals log reviewed. Vitals checked (BP, HR, RR, SPO2), and ICE score calculated. Subject will remain in apartment if no criteria for admission are met.
5.

Wearable device details: Subjects are trained to apply the devices which comprises of a patch that is applied on the left anterior chest, a blood pressure cuff that they will apply intermittently on the forearm, and a pulse oximeter that they will apply intermittently to the digits. They will wear the patch continuously but only apply the BP cuff and pulse oximeter at specific times as stated in the chart above. If patient fails to apply the BP cuff and pulse oximeter at the time stipulated, a vendor systems generated reminder will go to them. Any alerts issued by vendor can be viewed by the PI and all authorized users of the program. Data are recorded in the device database and are for research only but are accessible by specific clinical trial staff. Please see appendix G for more details
Telemedicine details: Subject and NP will activate the telemedicine App in their electronic device. Family will obtain vital signs (BP, HR, RR, SPO2) and provide NP with the figures. NP will also review the previous vital signs. Review of system questions are asked, and the answers given by subject recorded. Neurological assessment will be done, and ICE score calculated.

6.3.5. Criteria for Hospital Admission

1. Fever ≥102° F or higher, or fever 100.4 to < 102 with a change in status (e.g. hypotension, altered mental status or other end organ dysfunction). Fever < 102 alone without other symptom can be closely monitored in the outpatient setting per written institution guidelines. [10, 11]

2. Hemodynamic instability: (any of the following) Hypotension that requires IV fluids, MAP < 20% baseline or SBP < 90 mmHg or HR > 130/min

3. Hypoxia with SPO2 < 90%

4. Abnormal neurological function (grade 1 or higher ICANS) based on the ICE score as stated on Table 3

5. Other criteria at the discretion of the covering physician (discussed with PI).

Subjects that meet the criteria specified above will be admitted either as observation or inpatient depending on the severity of symptoms.

The following will trigger admission to observation status: Grade 2 CRS responding to fluids and hypoxia responding to supplemental oxygen by nasal cannula. Such subjects will be reviewed by treating physician who may recommend that they may be discharged to continue outpatient monitoring if there is resolution of symptoms. If the same symptom

occurs again the admission may be changed to inpatient status and they will remain inpatient until toxicity has returned to grade 1.

Any reduction in ICE score will prompt an observation admission. If the symptom completely resolves with intervention, subject can be discharged. However, if symptom persist for 12 – 24 hours the admission will be changed to inpatient status.

Laboratory parameters will not be used as the sole criteria to admit a subject but will be reviewed alongside clinical data.

6.3.6. Procedure for Hospital Admission

Once criteria for admission are met, NP will notify subject to report to the outpatient clinic (daytime admission) or myelosuppressive floor as a direct admission (night-time admission). NP will discuss case with the HCT attending, place orders as appropriate (IV fluid, tocilizumab, steroids, or antibiotics) and finalize management plan that is shared with the inpatient nurse to prepare.

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6.4. Toxicity Management

To date, the following important risks have been identified with YESCARTA: cytokine release syndrome (CRS), neurologic toxicities, infections, hypogammaglobulinemia, and cytopenias. Refer to the current IB version 10.0 for details (e.g. Section 6) regarding these events and management guidance.

Table 2. ASTCT Cytokine Release Syndrome (CRS) Consensus Grading

CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever[a]	Temperature ≥ 38° C	Temperature ≥ 38° C	Temperature ≥ 38° C	Temperature ≥ 38° C
with				
Hypotension	None	Not requiring Vasopressors.	Requiring a vasopressor with or without vasopressin.	Requiring multiple vasopressors (excluding vasopressin).
And/or[b]				
Hypoxia	None	Requiring low-flow nasal cannula[c] or blow-by.	Requiring high-flow nasal cannula[c], facemask, nonrebreather mask, or Venturi mask.	Requiring positive pressure (eg, CPAP, BiPAP, intubation and mechanical ventilation).

Notes:

a. Fever is defined as temperature ≥ 38°C not attributable to any other cause. In patients who have CRS then receive antipyretic or anticytokine therapy such as tocilizumab or

corticosteroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.

b. CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a patient with temperature of 39.5° C, hypotension requiring 1 vasopressor, and hypoxia requiring low-flow nasal cannula is classified as Grade 3 CRS.

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

Table 3. ASTCT Consensus Grading for Neurologic Events

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE Score[a]	7-9	3-6	0-2	0 (patient is unarousable and unable to perform ICE).
Depressed level of consciousness[b]	Awakens Spontaneously.	Awakens to Voice.	Awakens only to tactile Stimulus.	Life-threatening prolonged seizure (> 5 min); or Repetitive clinical or electrical seizures without return to baseline in between.
Seizure	N/A	N/A	Any clinical seizure focal or generalized that resolved rapidly or nonconvulsive seizures on EEG that resolve with intervention.	Life-threatening prolonged seizure (> 5 min); or Repetitive clinical or electrical seizures without return to baseline in between.
Motor finding[c]	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or Paraparesis.
Elevated ICP / Cerebral edema	N/A	N/A	Focal/local edema on neuroimaging[d]	Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing; or cranial nerve VI palsy; or papilledema; or Cushing's triad.

Notes: ICANS grade is determined by the most severe event (ICE score, level of consciousness, seizure, motor findings, raised ICP/cerebral edema) not attributable to any other cause; for example, a patient with an ICE score of 3 who has a generalized seizure is classified as Grade 3 ICANS.

a. A patient with an ICE score of 0 may be classified as Grade 3 ICANS if awake with global aphasia, but a patient with an ICE score of 0 may be classified as Grade 4 ICANS if unarousable.

b. Depressed level of consciousness should be attributable to no other cause (eg, no sedating medication).

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

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

Table 4. Immune Effector Cell-associated Encephalopathy (ICE) Score

Task	Direction	ICE Score
Orientation	State: year, month, city, hospital	4
Naming	Name: 3 objects	3
Following simple commands	Follow: Simple command	1
Writing	Ability to write a simple sentence	1
Attention	Count: Backwards from 100 by 10's	1

Notes: ICE Score: 10, no impairment; 7-9, Grade 1 ICANS; 3-6, Grade 2 ICANS; 0-2, Grade 3 ICANS; 0 due to patient unarousable and unable to perform ICE assessment, Grade 4 ICANS.

7. STUDY PROCEDURES

7.1. Informed Consent

Before a subject's participation in the clinical study, the investigator is responsible for obtaining written informed consent from the subject after adequate explanation of the study design, anticipated benefits and the potential risks. Subjects should sign the most current IRB/IEC approved ICF prior to any study specific activity or procedure is performed.

The consent process and the subject's agreement or refusal to participate in the study is to be documented in the subject's medical records. If the subject agrees to participate, the ICF is to be signed and personally dated by the subject and by the person who conducted the informed consent discussion. The original signed ICF will be retained in accordance with institution policy and IRB/IEC requirements with a copy of the ICF provided to the subject.

7.2. Screening

Investigative site will maintain a log of all screened. Information collected in the screening log should include limited information, such as the date of screening, date the subject was enrolled, or the reason for why the subject failed screening. Subjects who meet the eligibility criteria listed above in **Section 5** and who commence leukapheresis will be enrolled in the study. If subject fails to meet the eligibility criteria, they should be designated as a screen failure on the subject screening log with the reasons for failing screening noted.

7.3. Study Assessments

1. Medical history and disease assessment.
2. Physical examination, including height and weight. It is recommended that subjects with symptoms of central nervous system malignancy, such as new onset severe headaches, neck stiffness, or any focal neurologic findings on physical exam, have a lumbar puncture for examination of cerebral spinal fluid (CSF).

3. Vital signs, including blood pressure, heart rate, and temperature.

4. ECOG performance status.

5. Baseline PET-CT of the neck, chest, abdomen, and pelvis:

    a. PET-CT performed after the subject's last line of therapy and prior to signing the informed consent may be used.

    b. If a subject receives bridging therapy, a repeat PET-CT is recommended to establish a new baseline.

6. Bone marrow aspirate/biopsy as needed (if not done within 12 months of screening).

7. Laboratory tests (may be drawn anytime between signing of informed consent and prior to the start of lymphodepleting chemotherapy):

    a. Chemistry panel
    b. Complete blood count (CBC) with differential
    c. β-HCG pregnancy test (serum or urine) on all women of childbearing potential
    d. C-reactive protein (CRP)
    e. Blood draws for cytokines and PBMC.

8. AE and SAE reporting (see below **Section 10**).

9. Concomitant medications documentation and previous cancer treatment history.

7.4. Physical Exam, Vital Signs, Performance Status, and ICANS Score

A full neurological assessment including ICE score will be completed during screening to establish a baseline. Subsequent post-baseline assessments will be performed before as specified in the SOA.

7.5. Cardiac Function

Cardiac function, as measured by left ventricular ejection fraction (LVEF), and electrocardiogram (ECG) will be assessed during the screening period to confirm study eligibility.

7.6. Bone Marrow Biopsy if not previously done

A bone marrow aspirate/biopsy will be performed at screening, if not previously performed within 12 months of signing consent, to assess bone marrow involvement.

7.7. Lumbar Puncture

Subjects with symptoms of central nervous system malignancy, such as new onset severe headaches, neck stiffness, or any focal neurologic findings on physical exam, will have lumbar puncture performed at the screening visit for examination of CSF.

7.8. Disease response Assessment

PET with non-contrast CT scan will be done as SOC as from day + 30. Response assessment per Cheson 2014.[12]

7.9. Laboratory

The below samples will be collected at the time points indicated in the SOA. Additional samples (e.g., blood, urine, CSF, tissue, etc.) may be collected as needed for further safety testing:

1. Sodium (Na), potassium (K), chloride (Cl), total CO2 (bicarbonate), creatinine, glucose, blood urea nitrogen (BUN) or urea (if BUN test cannot be analyzed by the local lab), albumin, calcium total, magnesium total (Mg), inorganic phosphorus, alkaline phosphatase, ALT/glutamic-pyruvic transaminase (GPT), AST/glutamic-oxaloacetic transaminase (GOT), total bilirubin, direct bilirubin, lactate dehydrogenase (LDH), phosphorus and uric acid.
2. C-reactive protein (CRP) ferritin.
3. Complete blood count (CBC) with differential and platelet count.
4. A urine or serum sample will be collected and assessed locally for females of childbearing potential. If the screening pregnancy test is positive, the subjects should not be enrolled.

7.10. Correlative sample storage for potential future biomarker analysis

Biomarker analysis will be performed on blood and tumor samples to evaluate pharmacodynamic markers for Yescarta.

Correlative laboratory tests include:

1. Cytokine panel (including IL-1, IL-2, IL-6, IL-10, IL-15, granzyme B, TNF, IFN gamma, MCP1, GMCSF), CAR T cell quantification at day -5, 0, 1, 2, 3, 4, 7, 14, 30 (day 30 +/- 3 days)
2. CBC with differentials, ALC, monocyte count, LDH, chemistry (CMP including calcium, LDH, uric acid, phosphorus, magnesium), fibrinogen, CRP, ferritin
3. Product attributes, transduction rate, viability, IFN gamma in culture, pre-infusion doubling time
4. Optional paired CSF samples at day -5 and day +1. Optional paired tissue biopsy at day -5 and 2. We will make every effort to collect relapse biopsy specimen to better understand the mechanisms of tumor escape.
5. T cell elispot analysis for CART cell immunogenicity by peripheral blood at apheresis, day 30 (+/- 3 days), month 3, 6 and 12
6. Lymphocyte subsets to interrogate the pattern of recovery of B and T cells including the pattern of CD4 lymphopenia. Collect at apheresis, day zero, day 30 (+/- 3 days), months 3, 6 and 12
7. Collect CSF specimens in subjects with grade ≥2 ICANS when feasible. Correlative testing will be done at the end of the study based on a mutually agreed upon plan between Vanderbilt and Kite translational research

PBMC, serum and plasma are collected at specific time points as stated above. PBMCs are cryopreserved per lab manual and will be sent to Kite in batches. Samples will be analyzed at the end of the study for clues as to what series of parameters may be predictive of need for more care including hospitalization.

The samples will be collected per SOA and batch run at the end of the study. We will retrospectively check to see if any specific lab parameter may be predictive of need for more care including hospitalization.

7.11. Description of Study Periods

Investigative sites will maintain a log of all screened subjects who were reviewed and evaluated for study participation. Information collected on the screening log should include limited information such as the date of screening, date the subject was enrolled or the reason for why the subject failed screening.

7.11.1. Screening

The screening period begins on the date the subject signs the IRB/IEC approved ICF and continues through confirmation of enrollment. Informed consent must be obtained before completion of any non-standard of care study specific procedures. After written informed consent has been obtained, subjects will be screened to confirm study eligibility and participation. Only subjects who meet the eligibility criteria listed above in protocol **Section 5** and who commence leukapheresis will be enrolled in the study.

The following assessments/procedures are to be completed during the screening period at the time points outlined in the SOA:

1. Medical history and disease assessment.
2. Physical examination including height and weight.
3. Subjects with symptoms of central nervous system malignancy such as new onset severe headaches, neck stiffness, or any focal neurologic findings on physical exam will have lumbar puncture for examination of cerebral spinal fluid.
4. Vital signs, including blood pressure, heart rate, oxygen saturation, and temperature.
5. ECOG performance status.
6. ECG.
7. ECHO for confirmation of normal cardiac function (e.g., LVEF) and pericardial effusion assessment

8. Imaging Studies with PET with non-contrast CT scan to confirm measurable disease. CT chest, abdomen and pelvis is acceptable as clinically indicated.

9. Brain MRI.

10. Baseline PET with non-contrast CT scan of the neck, chest, abdomen and pelvis:
    a. PET with non-contrast CT scan performed following the subjects last line of therapy and prior to signing the consent may be used for confirmation of measurable disease. CT chest, abdomen and pelvis is acceptable as clinically indicated
    b. If PET with non-contrast CT scan is performed > 28 days prior to the initiation of lymphodepleting chemotherapy and if subject receives any anti-cancer therapy between screening and lymphodepleting chemotherapy, the scans must be repeated to establish a new baseline. CT chest, abdomen and pelvis is acceptable as clinically indicated
11. Bone marrow aspirate/biopsy as needed (if not done at initial diagnosis or between diagnosis and screening).
12. Laboratory tests:
    a. Chemistry panel
    b. CBC with differential.
13. β-HCG pregnancy test (serum or urine) on all women of child-bearing potential

7.11.2. Enrollment/Leukapheresis

Before leukapheresis commences, the following criteria must be met. If leukapheresis is delayed beyond 5 days, baseline CBC with differential and chemistry panel must be repeated to verify eligibility.

1. No evidence or suspicion of an infection.
2. Corticosteroid therapy at a pharmacologic dose (≥5 mg/day of prednisone or equivalent doses of other corticosteroids) and other immunosuppressive drugs must be avoided for 7 days prior to leukapheresis.
3. Once a subject commences leukapheresis, the subject will be considered enrolled into the study.

The following procedures/requirements will occur on the leukapheresis collection day and as outlined in the SOA:

1. Vital signs, including blood pressure, heart rate, oxygen saturation, and temperature.
2. Weight.

3. Laboratory tests (to be drawn prior to leukapheresis, on the day of or day before leukapheresis):

    a. Chemistry panel

    b. CBC with differential, CRP, ferritin, LDH

    c. Anti-CD19 CAR T cells

    d. Lymphocyte subsets

    e. Cytokine levels

    f. Anti-YESCARTA antibodies.

4. Adverse/Serious Adverse Event reporting.
5. Concomitant medications documentation.

7.12.3. Requirements for Initiating Lymphodepleting Chemotherapy

Lymphodepleting chemotherapy and YESCARTA infusion should only be initiated after it is reasonably assured that cell infusion can safely proceed. Subject will have a mini screen to ensure that they are able to be treated outpatient before proceeding.

If temperature rises above 38°Celsius or CRP above 100 mg/L within 72 hours of lymphodepleting chemotherapy, additional testing must be performed with satisfactory results before proceeding.

The subject must not have received systemic antimicrobials for the treatment of known or suspected infection within 48 hours before lymphodepleting chemotherapy (prophylactic use of antimicrobials is allowed).

Treatment course of any antimicrobials given for known or suspected antecedent infection should be completed as appropriate before stopping or switching to prophylactic antimicrobials.

If the subject is confirmed to have an infectious process for which antimicrobials are not available (e.g., viral pneumonia), the infection must be clinically resolved as determined by the investigator and in consultation with infectious disease service (if applicable).

The most recently collected blood, urine, or other body fluid cultures must show no growth for at least 48 hours, and any other infectious workup performed (e.g., bacterial, viral serologies, PCR, stood studies, imaging studies) must be negative. If clinical suspicion is for an infection for which cultures are unlikely to be positive within 48 hours (e.g., fungal infection), adequate time must be allowed for cultures to become positive.

Once the above criteria are met, then the subject can proceed with lymphodepleting chemotherapy.

7.12.4. Lymphodepleting Chemotherapy Administration

The following procedures will be completed during Day –5 to Day –3 as listed in the SOA:

- Vital signs, including blood pressure, heart rate, oxygen saturation, and temperature
- Laboratory tests (to be drawn prior to chemotherapy)
- Chemistry Panel
- CBC with differential
- Fludarabine and cyclophosphamide administration
- Adverse/Serious Adverse Event reporting
- Concomitant medications documentation.

7.12.5. Requirements for Initiating YESCARTA Infusion

These are the same as for lymphodepleting chemotherapy (i.e. above **Section 7.12.3**).

If the YESCARTA infusion is delayed > 2 weeks (14 days) from the planned infusion date, established institutional standards should be followed regarding the need for repeat lymphodepleting chemotherapy.

7.12.6. Monitoring After YESCARTA Infusion

All subjects will receive YESCARTA infusion at a healthcare facility followed by close monitoring for signs and symptoms of CRS and neurologic toxicities. Subjects may be hospitalized at any time post infusion and be observed for CRS and neurologic toxicities in the hospital setting, if deemed appropriate by the investigator.

If subjects are hospitalized, subjects should not be discharged from the hospital until all YESCARTA related non-hematological toxicities return to ≤ Grade 1 or return to Baseline as determined by the treatment team. Subjects may be discharged with non-critical and clinically stable or improving toxicities (e.g., renal insufficiency) even if > Grade 1, if deemed appropriate by the investigator.

Subjects should be instructed to remain within proximity of the clinical study site for at least 4 weeks following YESCARTA infusion. Subjects and their family members/caregivers should be educated on potential CRS and neurologic symptoms, such as fever, dyspnea, confusion, aphasia, dysphagia, somnolence, encephalopathy, ataxia, or tremor.

Subjects or their family members/caregivers should be instructed to immediately contact the treating investigator or seek immediate medical attention if any of these symptoms develop.

During this period, the following procedures will be completed at the time points outlined in the SOA.

7.12.7. Post-treatment Assessment Period

After completing YESCARTA infusion, all subjects will be followed in the post-treatment assessment period. Counting from Day 0 (YESCARTA infusion), subjects will return to the clinic at the Intervals stated in the SOA.

7.12.8. Long-term Follow-up Period

All enrolled subjects will be followed in the long-term follow-up period for survival and disease status. Subjects will begin long-term follow-up after completion of the Day 30 visit.

8. SCHEDULE OF ASSESSMENTS (SOA)

Protocol Activities	Screening (≤ 28 days prior to enrollment)	Enrollment / Leukapheresis	Bridging Therapy	Preparation for Lymphodepletion	Lymphodepleting Chemotherapy					YESCARTA	Post-Treatment Follow-Up						
					Days					Day 0	Days 1-14 (QD)	Day 21 (± 3d)	Day 30 (±3d)	Month (± 7d)			
					-5	-4	-3	-2	-1					2	3	6	9, 12
Clinical Assessments																	
Consent & eligibility	X																
ECOG performance status & medical history	X			X													
Quality of Life (QOL) questionnaire	X[13]												X		X[14]	X[14]	X[14]
Height (only at screening) & weight	X	X		X													
Vital signs (BP, HR, O2 sat, Temp)	X	X		X	X	X	X			X	X	X	X	X	X	X	
Physical exam	X			X						X	X	X	X	X	X	X	
Neuro assessment (including ICE score)[1]	X			X						X	X		X	X	X		
Targeted con meds & AE/SAEs[2]	X	X		X	X	X	X	X	X	X	X	X	X				
Laboratory Assessments																	
CBC with differential, platelets	X	X		X	X	X	X			X	X	X	X		X		
Chemistry panel (CMP plus LDH, uric acid & phosphorus, mag	X	X		X	X	X	X			X	X	X	X		X		
Fibrinogen	X			X	X					X	X	X	X				
CRP and ferritin	X	X		X	X					X	X	X	X		X		
Pregnancy test (blood or urine)	X			X													
ECHO and 12-lead ECG	X																
Disease Assessments																	
Archival tissue[3]	X																
Lumbar puncture (if clinically indicated)[4]	X									X							
Bone marrow biopsy (if clinically indicated)	X																
Optional paired tissue biopsy[5]					X						Day 2						
Optional paired CSF sample					X						Day 1						
Brain MRI or CT[16]	X																
PET/CT (disease status assessment)[6]	X[6]			X[6]									X		X	X	

Protocol Activities	Screening (≤ 28 days prior to enrollment)	Enrollment / Leukapheresis	Bridging Therapy	Preparation for Lymphodepletion	Lymphodepleting Chemotherapy					YESCARTA	Post-Treatment Follow-Up						
					Days					Day 0	Days 1-14 (QD)	Day 21 (± 3d)	Day 30 (±3d)	Month (± 7d)			
					-5	-4	-3	-2	-1					2	3	6	9, 12
Protocol Activities (continued)	**Screening (≤ 28 days prior to enrollment)**	**Enrollment / Leukapheresis**	**Bridging Therapy**	**Preparation for Lymphodepletion**	**Lymphodepleting Chemotherapy**					**YESCARTA**	**Post-Treatment**						
					Days					**Day 0**	**Days 1-14 (QD)**	**Day 21 (± 3d)**	**Day 30 (±3d)**	**Month (± 7d)**			
					-5	**-4**	**-3**	**-2**	**-1**					**2**	**3**	**6, 12[12]**	
Additional Blood Collections																	
T Cell Elispot Analysis		X											X		X	X	
Lymphocyte subsets (B and T)		X								X			X		X	X	
Cytokines[7]		X			X					X	1-4, 7 & 14		X				
Anti-CD19 CAR T cells (flow cytometry)		X									7, 14		X		X		
Replication competent retrovirus (RCR) detection										X					X	X	
MRD assessment[11]		X											X		X	X	
Treatment																	
Leukapheresis		X															
Bridging therapy[8]			X														
Cyclophosphamide / fludarabine					X	X	X										
YESCARTA infusion										X							
Dexamethasone[15]										Days 0, 1, 2							
Tocilizumab[9]										PRN							
Levetiracetam (Keppra)[10]										PRN							

Notes:

1. Immune Effector Cell-associated Encephalopathy (ICE) score per **Table 4 / Section 6.4** to be included in the neurological exam.

2. Targeted review of non-serious and serious Adverse Events of Special Interest (AESI, as defined in protocol **Section 10.6**) and concomitant medications used to prevent or treat such events will be conducted as indicated and until at least 30 days after initiation of YESCARTA infusion.
3. Hematopathology review of archival tissue slides to confirm diagnosis.
4. Lumbar puncture (LP) at screening if clinically indicated. LP also to be done for new onset neurological symptom(s).
5. Optional paired samples of tumor on Day -5 (before lymphodepleting chemo) and Day 2 (48 hours post CAR T infusion).
6. PET scan can be replaced with a CT scan in cases where a PET scan is out of window and a second PET scan cannot be obtained or as clinically indicated. Preparation for lymphodepleting chemotherapy requires new PET with non-contrast CT scan if debulking therapy given and if the first screening images are > 28 days. CT chest, abdomen and pelvis can be substituted for PET as clinically indicated
7. Blood for cytokine levels, PBMC and quantification of CAR T cells at screening, Days – 5, 0, 1, 2, 3, 4, 7, 14, 30 (±3 days).
8. Bridging therapy is optional as determined by the treating physician and will be given after apheresis. See **Section 6**.
9. Tocilizumab may be given between Day 0-14 in the event of cytokine release syndrome (CRS).
10. Keppra may be given from Day 0-28 and then taper to off.
11. Plasma sample for MRD assessment by clonoseq and capseq.
12. 12-Month post-treatment visit is for additional blood collection tests only as noted in the schedule of assessments.
13. QoL survey (Subject-Reported Outcomes Measurement Information System (PROMIS)) 14 days prior to lymphodepletion <u>+/- 5 days</u>
14. QoL survey 3, 6. 9 and 12 months post-treatment follow up <u>+/- 14 days</u>
15. Dexamethasone 10mg should be given PO before axicabtagene ciloleucel infusion on Day 0. Dexamethasone can be given at any time on Days 1 and 2.
16. Brain imaging by MRI or CT if clinically indicated. CT acceptable if MRI is not able to be obtained

9. SUBJECT WITHDRAWAL

Subjects have the right to withdraw from the study at any time and for any reason without prejudice to their future medical care by the physician or at the institution.

Subjects can decline to continue to receive study required treatment and/or other protocol required procedures at any time during the study but continue to participate in the study. This is referred to as partial withdrawal of consent.

If partial withdrawal of consent occurs, the investigator must discuss with the subject the appropriate process for discontinuation from investigational product, study treatment or other protocol required therapies and must discuss options for continued participation, completion of procedures and the associated data collection as outlined in the SOA. The level of follow up and method of communication should also be discussed between the research staff and the subject and documented in the source documents.

Withdrawal of full consent from a study means that the subject does not wish to receive further protocol required therapy or undergo procedures and the subject does not wish to continue further study follow-up. Subject data collected up to withdrawal of consent will be retained and included in the analysis of the study, and where permitted by local regulations, publicly available data (death records) can be included after withdrawal of consent. The investigator is to discuss with the subject appropriate procedures for withdrawal from the study.

Public records, such as those establishing survival status, if available, may be searched to obtain survival data for any subject for whom the survival status is not known. Autopsy reports may also be retrieved to confirm status of disease at the time of death.

The investigator and/or sponsor can also decide to withdraw a subject from the investigational product and/or other protocol-required therapies, protocol procedures, or the study as a whole or at any time prior to study completion.

9.1. Reasons for Removal from Treatment

Reasons for removal from protocol required investigational products or procedures include any of the following:

1. Adverse Event
2. Subject request
3. Product not available
4. Lost to Follow-up
5. Death
6. Decision by sponsor.

9.2. Reasons for Removal from Study

1. Reasons for removal of a subject from the study are as follows:
2. Subject withdrawal of consent from further follow-up
3. Investigator decision
4. Lost to follow-up
5. Death.

10.1 General Considerations

Information on adverse events, whether serious or not, whether reported by the participant, directly observed, or detected by physical examination, laboratory test or other means, will be collected, recorded, followed and reported as described in the following sections.

The therapy administered in this trial – YESCARTA (axicabtagene ciloleucel) – is an approved treatment for the patient population eligible to participate in this study. Therefore, collection of data regarding adverse events and serious adverse events will be limited in this study:

- After informed consent but prior to initiation of YESCARTA infusion, serious and non-serious adverse events should be reported only if possibly, probably or definitely attributed by the patient's study physician to a protocol-mandated research procedure or intervention.
- Any serious adverse event that occurs ≤ 30 days after initiation of YESCARTA, regardless of causality to participation in the study, must be reported to the Study Coordinator fashion as directed below (Reporting Procedures).
- For purposes of this study, **cytokine release syndrome**, **neurological events, hematological severe infections greater than or equal to Grade 3, autoimmune events, and secondary malignancy events** are considered **Adverse Events of Special Interest (AESI)**.
- From the time of initiating YESCARTA infusion and until at least 30 days after initiation of the YESCARTA infusion, all adverse events of special interest (AESI) experienced by a participant must be collected in the study data, regardless of attribution to participation in the study.

  Additionally (as addressed below in **Section 10.6)**, if an event of special interest (AESI) is also a non-serious adverse event (AE) greater than or equal to Grade 3, or a serious adverse event (SAE) of any grade, the AESI must also be reported in an expedited manner by the site to the Study Coordinator, within 24 hours of the investigator becoming aware of the event (i.e. a 'substantial' AESI must not only be conventionally recorded in the general study data/electronic case report form, but also reported via expedited alert).

- During the 30-day follow-up period (i.e. the 30 days following initiation of the YESCARTA infusion), non-serious adverse events which are not adverse events of special interest (AESI) are required to be recorded in the study data only if, in the opinion of the investigator, there is a reasonable possibility the event is attributable to a protocol-mandated research procedure or intervention. For example, provided they are not adverse events of special interest (AESI), non-serious adverse events related to disease, standard-of-care YESCARTA or the next phase of the patient's disease treatment or management are not required to be recorded in the study data. All serious adverse events (SAEs) and adverse events of special interest (AESI) occurring within the 30-day follow-up period must be reported, regardless of suspected causality.
- Participants who experience an ongoing serious adverse event (SAE) or an adverse event of special interest (AESI) > 30 days after initiation of YESCARTA deemed possibly, probably or definitely related to YESCARTA, will continue to be contacted by a member of the study team until the event is resolved, stabilized, or determined to be irreversible or not clinically significant by the participating investigator.

Participants should be instructed to report any serious post-study event(s) that might reasonably be related to participation in this study. The investigator should notify the IRB and the Study Coordinator of any unanticipated death or adverse event occurring after a participant has discontinued or terminated study participation that may reasonably be related to the study.

10.3 Grading of Adverse Events

Adverse events will be graded according to the NCI's Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 5.0, dated November 27, 2017, currently locatable via the following URL:
<https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf>.

If events are not listed in the CTCAE, severity may be designated as mild, moderate, severe, life-threatening, or fatal which respectively correspond to Grades 1, 2, 3, 4, and 5 on the NCI CTCAE, with the following definitions:

- Mild: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated;
- Moderate: Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL) such as preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc;
- Severe: Medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL such as bathing, dressing and undressing, feeding self, using the toilet, taking medications;

- Life-threatening: Urgent intervention indicated to prevent risk of death present at the time of the event;

- Fatal: An event that results in the death of the patient.

10.4.1. **Adverse Event (AE)**

An adverse event is any undesirable sign, symptom or medical condition or experience that develops or worsens in severity after starting the first dose of study treatment or any procedure specified in the protocol, even if the event is not considered to be related to the study.

Abnormal laboratory values or diagnostic test results constitute adverse events only if they induce clinical signs or symptoms or require treatment or further diagnostic tests.

10.4.2. **Serious Adverse Event (SAE)**

A serious adverse event is an undesirable sign, symptom or medical condition which:

- Is fatal or life-threatening;
- Requires or prolongs inpatient hospitalization;
- Results in persistent or significant disability/incapacity;
- Constitutes a congenital anomaly or birth defect; or
- Jeopardizes the participant and requires medical or surgical intervention to prevent one of the outcomes listed above.

Events not considered to be serious adverse events are hospitalizations for:

- Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition, or for elective procedures.
- Admission for closer monitoring for known side effects of therapy such as cytokine release syndrome and neurological events do not qualify as an SAE.
- Elective or pre-planned treatment for a pre-existing condition that did not worsen.
- Emergency outpatient treatment for an event not fulfilling the serious criteria outlined above and not resulting in inpatient admission.

- Respite care.

10.4.3. **Expectedness**

Expected: Expected adverse events are those that have been previously identified as resulting from administration of the agent. For the purposes of this study, an adverse event is considered expected when it appears in the current adverse event list, the Investigator's Brochure, the package insert or is included in the informed consent document as a potential risk.

Unexpected: An adverse event is considered unexpected when it varies in nature, intensity or frequency from information provided in the current adverse event list, the Investigator's Brochure, the package insert or when it is not included in the informed consent document as a potential risk.

10.4.4. **Attribution**

Attribution is the relationship between an adverse event or serious adverse event and the study treatment. Attribution will be assigned as follows:

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

10.5. Reporting Procedures

10.5.1. **General Considerations**

Investigators should use correct medical terminology/concepts when reporting Aes or SAEs, and avoid colloquialisms and abbreviations. If known at the time of reporting, a diagnosis should be reported rather than individual signs and symptoms (e.g. record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, it is acceptable to report the information that is currently available. If a diagnosis is subsequently established, it should be reported as follow-up information.

All deaths that occur during the protocol-specified AE reporting period, regardless of attribution, will be reported to relevant bodies including Kite Pharmacovigilance, Vanderbilt, and CIBMTR. When recording a death, the event or condition that caused or contributed to the fatal outcome should be reported as the single medical concept. If the cause of death is unknown and cannot be ascertained at the time of reporting, report "Unexplained Death." Deaths that occur during the protocol specified adverse event reporting period that are attributed by the investigator solely to progression of disease should be recorded only in the study eCRF and not reported as an SAE.

A pre-existing medical condition is one that is present prior to initiation of protocol specified treatment. Such conditions should be reported as medical and surgical history. A pre-existing medical condition should be re-assessed throughout the trial and reported as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When reporting such events, it is important to convey the concept that the pre-existing condition has changed by including applicable descriptors (e.g., "more frequent headaches").
Any AE that results in transfer to the Intensive Care Unit (ICU) should be documented and reported as an SAE. If a patient is hospitalized to undergo a medical or surgical procedure as a result of an AE, the event responsible for the procedure, not the procedure itself, should be reported as the SAE. For example, if a patient is hospitalized to undergo coronary bypass surgery, record the heart condition that necessitated the bypass as the SAE.

Hospitalizations for the following reasons do not require reporting:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for pre-existing conditions; or
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study; or
- Hospitalization or prolonged hospitalization for scheduled therapy of the target disease of the study.

10.5.2. **Serious Adverse Events**

All serious adverse events, regardless of causality to study drug, will be reported to the Principal Investigator and the Study Coordinator at the institution.

All serious adverse events must be reported to the Study Coordinator within 24 hours of the investigator becoming aware of the event. Events should be reported using the Vanderbilt SAE form, located in the packet of supplemental forms. This form must be fully completed and emailed (preferred), faxed, or scanned to the Study Coordinator.

The Study Coordinator will disseminate information regarding serious adverse events to the participating site as described in FDA guidance only in the case that the event(s) is/are unexpected, and is/are believed to be related (i.e., possibly, probably or definitely) to the study device/medication. The Study Coordinator will be responsible for reporting of events to supporters, as appropriate (outlined below).

10.5.3. **Institutional Review Board**

All adverse events and serious adverse events will be reported to the IRB per current institutional standards. If an adverse event requires modification of the informed consent, these modifications will be provided to the IRB with the report of the adverse event. If an adverse event requires modification of the study protocol, these modifications will be provided to the IRB as soon as is possible.

10.5.4. **Reporting to Supporters**

Vanderbilt University Medical Center will notify the funder of any serious adverse event (SAE) that occurs during the reporting period as defined above in **Section 10.2**. Within 2 working days after the Study Coordinator initially receives the safety information from the site, the Study Coordinator will report the SAE (on the MedWatch, funder, or Vanderbilt SAE form approved by the study team and funder) to a point of contact specified by the funder – for example to **Kite/Gilead** via email at [redacted]. Follow-up SAE reports received by the Study Coordinator should be sent within 2 working days to the funder using the same procedure used for transmitting the initial report.

10.6. Adverse Events of Special Interest (AESI)

Selected non-serious and serious adverse events are also known as Adverse Events of Special Interest (AESI). **In this trial, adverse events of special interest include**:

- Neurological events ≥ Grade 3.
- Hematological severe infections ≥ Grade 3,
- Autoimmune events, and
- Secondary malignancy events,
- Cytokine release syndrome ≥ Grade 3.

Within the reporting period outlined above in Section 10.2 and according to SAE reporting procedures outlined in Section 10.5, all adverse events of special interest (AESI) meeting the following criteria must be reported in an EXPEDITED manner by the site to the Study

Coordinator within 24 hours of the investigator becoming aware of the event – regardless of attribution to participation in the study:

- AESI that is a non-serious adverse event (AE) ≥ Grade 3, or
- AESI that is a serious adverse event (SAE) of any grade.

11. STATISTICAL CONSIDERATIONS

11.1. General Analysis Plan

No formal hypothesis will be tested in this study. Data analysis will be descriptive. No group comparisons will be made. Continuous variable will be summarized using the minimum value, maximum value, 25^{th}, 50^{th} (median), and 75^{th} percentiles as well as the mean and standard deviation. Categorical variables will be summarized in frequency tables. [13-15] See appendix E for detailed statistical considerations.

11.2. Study Endpoints

11.2.1. **Primary Endpoints**

1. Number of subjects that remain an outpatient at 3, 7 and 30 days after YESCARTA infusion.
2. Time to requirement for inpatient hospitalization after YESCARTA infusion.

11.2.2. **Secondary Endpoints**

1. Incidence of Aes and clinically significant changes in safety lab values.
2. Incidence/grade of adverse events.
3. Incidence/grade of CRS and ICANS.
4. Incidence of steroid and/or tocilizumab administration.
5. YESCARTA treatment response rate.
6. Time to intervention defined as the time interval between when the call was made to admit the subject for an adverse event of interest and the time that specific intervention was given.
7. Rate of use of tocilizumab, corticosteroids, vasopressors.

11.2.3. **Exploratory Endpoints**

1. Levels of inflammatory cytokines in subject's serum before and after YESCARTA infusion.
2. Investigation for potential predictive markers for grade 3 or higher toxicity or need for hospitalization.
3. Modified NF symptom burden score for days 1-3 for each subject (appendix D)
4. Subject reported outcomes measured by Subject-Reported Outcomes Measurement Information System (PROMIS) [16, 17].

11.3. Sample Size

Twenty subjects will receive YESCARTA treatment at a maximum of two sites. Subjects who are unable to proceed with CART infusion and monitoring for 14 days on study will be replaced.

12. DATA SAFETY AND MONITORING

12.1. Data Management and Reporting

Participating institutions will collaborate with Vanderbilt for patient accrual. The Vanderbilt University Office of Research will be used as a central location for data processing and management. Vanderbilt University, with collaboration from a consortium of institutional partners, has developed a software toolset and workflow methodology for electronic collection and management of research and clinical trial data. REDCap (Research Electronic Data Capture) is a secure, web-based application that is flexible enough to be used for a variety of types of research. REDCap provides an intuitive user interface that streamlines project development and improves data entry through real-time validation rules (with automated data type and range checks). REDCap also provides easy data manipulation (with audit trails for reporting, monitoring and querying patient records) and an automated export mechanism to common statistical packages (SPSS, SAS, Stata, R/S-Plus). In addition to traditional data capture functionality, REDCap's survey capabilities are a powerful tool for building and managing online surveys. The research team can create and design surveys in a web browser and engage potential respondents using a variety of notification methods. All data collection projects rely on a thorough, study-specific data dictionary, defined by all members of the research team in an iterative, self-documenting process. This iterative development and testing process results in a well-planned and individualized data collection strategy.

REDCap servers are housed in a local data center at Vanderbilt, and all web-based information transmission is encrypted. REDCap was developed specifically around HIPAA-Security guidelines and is recommended to Vanderbilt researchers by both our Privacy Office and Institutional Review Board. REDCap has been disseminated for local use at more than 940 other academic/non-profit consortium partners in 75 countries. Vanderbilt leads the REDCap Consortium, which currently supports more than 99,000 projects and 128,000 users. More information about the consortium and system security can be found at http://www.projectredcap.org/.

12.2. Auditing and Monitoring

The Vanderbilt-Ingram Cancer Center (VICC) oversees patient safety and data monitoring for its investigator-initiated and NIH-NCI funded clinical trials through its Data and Safety Monitoring Committee (DSMC). The purpose of the DSMC is to ensure the efficient implementation and management of the VICC Data and Safety Monitoring Plan (DSMP). The Committee maintains authority to intervene in the conduct of studies as necessary to ensure clinical research performed at VICC achieves the highest quality standards.

The VICC DSMC meets on a quarterly basis and ad hoc to discuss data and safety monitoring of clinical trials and to oversee the VICC DSMP. Internal audits for compliance with adverse event reporting, regulatory and study requirements, and data accuracy and completion are conducted according to the VICC DSMP according to study phase and risk. The committee reviews all serious adverse events (SAE) on Vanderbilt sponsored investigator-initiated studies on a quarterly basis and provides DSMC SAE review reports to the Vanderbilt IRB.

The trial additionally will be monitored by the VICC Multi-Institutional Coordinating Center. The actual frequency of monitoring will depend on the enrollment rate and performance of the site. Monitoring will be conducted through onsite and/or remote monitoring, teleconferences with the Investigator and site staff, and appropriate communications by mail, fax, email, or telephone. The purpose of monitoring is to ensure that the study is conducted in compliance with the protocol, standard operating procedures (SOPs), and other written instructions, and to ensure the quality and integrity of the data.

During scheduled monitoring visits, investigators and the investigational site staff must be available to discuss the progress of the trial, make necessary corrections to case report form entries, respond to data clarification requests, provide required regulatory documents, and respond to any other trial-related inquiries of the monitor.

12.3. Data Handling and Record Keeping

An electronic case report form (eCRF) is required and must be completed for each included participant. The completed dataset should not be made available in any form to third parties, except for authorized representatives of appropriate Health/Regulatory Authorities, without written permission from Vanderbilt.

To enable evaluations and/or audits from health authorities and Vanderbilt, the site investigator agrees to keep records including: The identity of all participants (sufficient information to link records; e.g., hospital records), all original signed informed consent forms, copies of all source documents, and detailed records of drug disposition. To comply with international regulations, the records should be retained by the investigator in compliance with regulations.

Queries resulting from review of the eCRFs will be generated for the site and corrections will be made by the study site personnel. This will be done on an ongoing basis.

13. REGULATORY CONSIDERATIONS

13.1. Protocol Review and Amendments

Information regarding study conduct and progress will be reported to the Institutional Review Board (IRB) per current institutional standards.

The trial will not be initiated until there is approval by the local IRB of the protocol, informed consent document and any other material used to inform the patient about the nature of the

trial. The IRB should be duly constituted according to local regulatory requirements. The investigator will inform the IRB of the progress of the trial at least yearly.

Any changes to the protocol will be made in the form of a written amendment and must be approved by the sponsor-investigator and the local IRB prior to local implementation. All amendments will also be submitted as necessary to the FDA by the sponsor-investigator (or designee).

Protocol changes to eliminate an immediate hazard to a trial patient may be implemented by the investigator immediately. The investigator must then immediately inform the local IRB; and the sponsor-investigator (or designee), who will communicate as appropriate with the FDA.

The sponsor-investigator (or designee) is responsible for the coordination and development of all protocol amendments and will disseminate this information to the participating centers.

13.2. Informed Consent

The investigator (or designee) will explain to each participant the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved and any discomfort it may entail. Each participant will be informed that participation in the study is voluntary, that s/he may withdraw from the study at any time, and that withdrawal of consent will not affect subsequent medical treatment or relationship with the treating physician(s) or institution. The informed consent will be given by means of a standard written statement, written in non-technical language, which will be IRB approved. The participant should read and consider the statement before signing and dating it and will be given a copy of the document. No patient will enter the study or have study-specific procedures done before his/her informed consent has been obtained.

In accordance with the Health Information Portability and Accountability Act (HIPAA), the written informed consent document (or a separate document to be given in conjunction with the consent document) will include a subject authorization to release medical information to the study sponsor and supporting agencies and/or allow these bodies, a regulatory authority, or Institutional Review Board access to subjects' medical information that includes all hospital records relevant to the study, including subjects' medical history.

13.3. Confidentiality

It is the responsibility of the investigator to ensure that the confidentiality of all patients participating in the trial and all of their medical information is maintained. Case report forms (CRFs) and other documents submitted to regulatory authorities must not contain the name of a trial patient. All patients in the trial will be identified by a unique identifier which will be used on all CRFs and any other material submitted to regulatory authorities. All case report forms and any identifying information must be kept in a secure location with access limited to the study staff directly assisting with the trial.

13.4. Study Termination

The sponsor-investigator reserves the right to terminate the study at any site and at any time. Reasons for study termination may include, but are not limited to, the following:

- Investigator non-compliance with the protocol, GCP or regulatory requirements.
- Insufficient enrollment.
- Safety concerns.
- Decision by suppliers to modify or discontinue the availability, development or manufacture of protocol-indicated treatment.
- A request to discontinue the study by the IRB or recognized regulatory authority.

14. STUDY COORDINATION

14.1. Trial Compliance

This is an investigator-initiated study. The Principal Investigator, Olalekan O. Oluwole, MD, MPH (who may also be referred to as the Sponsor-Investigator), is conducting the study and acting as the sponsor. Therefore, the legal and ethical obligations of the Principal Investigator include both those of a sponsor and those of a principal investigator.

Vanderbilt is the Coordinating Center for this study. All aspects of the study will be carefully monitored by the Coordinating Center for compliance with applicable government regulations with respect to current GCP and standard operating procedures.

14.2. Changes to Protocol and Informed Consent Document

Any change to the protocol or informed consent document must be reviewed and approved by the investigator before being submitted to the Institutional Review Board/Independent Ethics Committee at participating institutions. Amendments should not be implemented until all necessary approvals have been obtained, except when necessary to eliminate an immediate hazard to study subjects.

14.3. Protocol Deviations

The Coordinating Center is responsible for implementing and maintaining quality assurance and quality control to ensure that studies are conducted according to the protocol, GCP, and all applicable regulatory requirements. A protocol deviation is any noncompliance with the protocol. Noncompliance can be on the part of the study participant, the investigator, or the study site staff. Deviations to the protocol are not permitted except when necessary to eliminate an immediate hazard to study subjects.

14.4. Monitoring and Quality Assurance

As the Coordinating Center, Vanderbilt has responsibilities to health authorities to take all reasonable steps to ensure the proper conduct of the study with regard to ethics, protocol adherence, integrity, validity of the data recorded on the CRFs, and adherence to regulations regarding Good Clinical Practice (GCP) and the protection of human subjects.

In accordance with applicable regulations, GCP, and Coordinating Center procedures, sites will be contacted prior to the start of the study to review with site staff the protocol, study

requirements, and their responsibilities to satisfy regulatory, ethical, and Coordinating Center requirements.

During the course of the study, the Coordinating Center will routinely monitor sites for protocol compliance, compare CRFs with original source documents from individual subjects, assess drug accountability, and ensure that the study is being conducted according to the pertinent regulatory requirements. The review of subject medical records will be performed in a manner to ensure that subject confidentiality is maintained. Monitoring visits will primarily be conducted remotely, and sites are required to provide the appropriate source documentation in order to allow for proper oversight per GCP. Investigators must agree to cooperate with the Coordinating Center to ensure that any problems detected are resolved.

14.5. Data Verification

Data will be collected via eCRFs and entered into the database per Coordinating Center guidelines. The Coordinating Center will check data accuracy by performing source data verification. Source data verification is a direct comparison of the entries made on the CRFs against the appropriate source documentation. This will be conducted remotely, with the possibility of on-site verification periodically. Discrepancies in the data will be brought to the attention of the investigator and/or the investigator's staff. Any necessary corrections will be made directly to the eCRFs or via queries by the investigator and/or the investigator's staff.

14.6. Study Documentation

Each participating site is responsible for submitting copies of all relevant regulatory documentation to the Coordinating Center. The required documents include but are not limited to the following: local IRB approvals (i.e., protocol, consent form, amendments, patient brochures, recruitment material, etc.), IRB membership rosters, summary of unanticipated problems or protocol deviations, and documentation of expertise of the investigators. The Coordinating Center will provide each participating site with a comprehensive list of the necessary documents. It is the responsibility of the participating sites to maintain copies of all documentation submitted to the Coordinating Center.

The requirements for data management, submissions, and monitoring are outlined below. The participating sites will submit all the research related information inclusive of:

- Source documents (patient registration list, CRF info, toxicity assessments, tumor measurements / responses, etc.) are required to be provided within 30 days of visit or 10 days in advance of a monitoring visit or audit,
- Essential Documents (IRB approval documents, financial disclosure forms, 1572, delegation of authority log, protocol training, etc.) are required to be provided within one week of receiving the updated documents.

Personnel from the VICC Clinical Trials Office will monitor the trial and may periodically visit the investigative site to assure proper conduct of the trial and proper collection of the data. The investigators at other sites will allow the monitor to review all source documents used in the preparation of the case reports.

14.7. Closure of the Study

The Coordinating Center reserves the right to discontinue a site at any time during the study for medical or administrative reasons such as:

- Unsatisfactory enrollment;
- GCP noncompliance;
- Inaccurate or incomplete data collection;
- Falsification of records;
- Failure to adhere to the study protocol.

14.8. Records Retention

U.S. FDA regulations (21 CFR §312.62[c]) require that records and documents pertaining to the conduct of this study, including CRFs, consent forms, laboratory test results, and medication inventory records, must be retained by each Principal Investigator for 2 years after marketing application approval. If no application is filed, these records must be kept 2 years after the study is discontinued and the applicable national and local health authorities are notified.

Following closure of the study, each participating center will maintain a copy of all site study records in a safe and secure location. The Coordinating Center will inform the investigator at such time that the records may be destroyed.

14.9. Publication

It is understood that any manuscript or releases resulting from the collaborative research must be approved by the sponsor-investigator and will be circulated to applicable participating sites/investigators prior to submission for publication or presentation.

17. REFERENCES

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APPENDICES

Appendix A: YESCARTA Patient and Caregiver Education

Appendix B: YESCARTA Caregiver Pre-Test

Appendix C: YESCARTA Caregiver Post-Test

Appendix D: Clinical Practice Guideline for Outpatient Management of Febrile Neutropenia in Patients Receiving Commercial CAR T-Cell Therapy

Appendix E: Detailed Statistical Considerations

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Appendix G: Biofourmis Wearable Device

Appendix A

Vanderbilt University Medical Center
YESCARTA Patient and Caregiver Education: Self-monitoring for CAR T toxicities

Date:

[redacted]

General consideration:
You are part of patient's care team and we need your help to monitor the patient's wellbeing while not in the clinic or hospital. It is very important that you pay attention to any new symptoms or signs and report to us immediately. Below is the summary common symptoms/signs of CAR T therapy associated toxicities. This is NOT a complete list and you should not hesitate to call us with any new issue which may arise while at home.

I. Vital Signs: equipment, testing, results

- What equipment will you use?
  - Blood Pressure Cuff – used to take patient's blood pressure and heart rate
  - Pulse Oximeter – used to measure patient's oxygen and heart rate
  - Thermometer – used to take patient's temperature
- How often will take vitals for patient
  - Patient will have vital signs done during clinic visits at **8am**
  - The caregiver will be responsible for vital signs at **6am, 12pm, 4:30, 10pm,**
- How will you report vital signs?
  - Patient will have a video conference call with night NP at **4:30pm and 10:00 PM** ± 1 hour for at least first 14 days after Car-T infusion
  - Patient will call night NP at 6am to report **6am** vital signs.

Things to monitor at Home:

II. Signs of Infection

- Fever: You will take your temperature **6am, 12pm, ≤10pm**,
  - A temperature higher than 100.3 F is a reason to call at any time
- Redness and/or tenderness around patient's venous catheter site
- Dizziness, shortness of breath, cough, altered mental status

III. Cytokine Release Syndrome (CRS)

- What is CRS?
  - This is an inflammatory process that impacts many organs. CRS typically occurs within first week after CAR-T infusion.
- What are CRS symptoms?
  - Fever
  - Chills
  - Dizziness/lightheadedness
  - Shortness of breath
  - Altered mental status
  - Low blood pressure (Please call if systolic blood pressure drops below ____ mm Hg)

  - Fast heart rate (Please call if hear rate is above 120 beats/min)
  - Low blood oxygen levels (Please call if pulse oxygen level fall below 90 %).
- How do we treat CRS?
  - Intravenous fluids
  - Supplemental Oxygen
  - Tocilizumab (medication to reverse CRS)
  - Steroids.

IV.Neurotoxicity

- What is Neurotoxicity?
  - This is a collection of symptoms that impact patient's mental status related to CAR T therapy administration.
- What are Neurotoxicity symptoms?
  - Confusion
  - Headache
  - Delirium (confused thinking and reduced awareness of environment, for example to time and place; usually with rapid onset)
  - Difficulty finding words/speaking
  - Difficulty following commands
  - Memory lapses
  - Hallucinations (seeing or hearing things which does not exist)
  - Dizziness
  - Tremors
  - Seizures/ convulsions
  - Lethargy (lack of energy and enthusiasm).
- How do we treat Neurotoxicity?
  - Steroids.

V. Monitoring

- How will the patient be monitored?
  - You will be seen every day in our Outpatient Transplant Unit (OTU) at 8:00am and a nurse will visit the apartment at 4:30pm ± 1 hour daily for 14 days after your CAR-T infusion (Day 0)
  - You will have your labs and vitals taken daily in clinic.
  - You will have a video conference telehealth visit with the night NP at 10pm. At that time, you will take your vital signs and answer questions.
  - You will take your vitals at 6am and then have a morning phone call with night NP to report overnight vital signs.
  - Once you are discharged from the OTU, you will transition to the CAR-T long term care clinic. This typically occurs between 14 and 30 days after CAR-T infusion.

Official Use only

Version date:	Approved by:

Appendix B

Vanderbilt University Medical Center
YESCARTA Caregiver Pre-Test

Date: **Subject ID:**

1. What temperature is considered serious and warrants a call to Vanderbilt?
    a. 100.0°F
    b. 99.5°F
    c. 100.4°F
    d. 97.6°F
2. Which symptom may mean the patient is experiencing neurotoxicity?
    a. Tremors
    b. Confusion
    c. Being extra sleepy
    d. All of the above
3. What times do we need the patient to connect to the telehealth monitoring system?
    a. 10:00 PM
    b. 2:00 AM
    c. 6:00 AM
    d. None of the above
4. Please perform 3 blood pressures on patient and write down values:
    a.
    b.
    c.
5. Please take the patient's temperature 3 times and write down values:
    a.
    b.
    c.
6. Please take patient's pulse oxygen levels and write down values:
    a.
    b.
    c.
7. Please check patient's heart rate and write down values:
    a.
    b.
    c.
8. What symptom may mean the patient is experiencing cytokine release syndrome (CRS)?
    a. Chills
    b. Low blood pressure
    c. Fever
    d. All of the above

Official Use only

Appendix Version Date:	Score:	Pass/Fail	Comment:	Reviewer's initials:

Appendix C

Vanderbilt University Medical Center
YESCARTA Caregiver Post-Test

Date: **Subject ID:**

1. What temperature is considered serious and warrants a call to Vanderbilt?
    a. 100.0°F
    b. 99.5°F
    c. 100.4°F
    d. 97.6°F
2. Which symptom may mean the patient is experiencing neurotoxicity?
    a. Tremors
    b. Confusion
    c. Being extra sleepy
    d. All of the above
3. What times do we need the patient to connect to the telehealth monitoring system?
    a. 10:00 PM
    b. 2:00 AM
    c. 6:00 AM
    d. None of the above
4. Please perform 3 blood pressures on patient and write down values:
    a.
    b.
    c.
5. Please take the patient's temperature 3 times and write down values:
    a.
    b.
    c.
6. Please take patient's pulse oxygen levels and write down values:
    a.
    b.
    c.
7. Please check patient's heart rate and write down values:
    a.
    b.
    c.
8. What symptom may mean the patient is experiencing cytokine release syndrome (CRS)?
    a. Chills
    b. Low blood pressure
    c. Fever
    d. All of the above

Official Use only

Score	Pass/Fail	Comment:	Reviewer's initials:

Appendix D

Suggested Guideline for Outpatient Management of Febrile Neutropenia in Patients Receiving Immune Effector-Cell Therapy

Modified Neutropenic Fever Symptom Burden (NFSB) score: Modified from MASCC

Introduction:

Prevention and appropriate management of febrile neutropenia (FN) is important because the rate of major complications (e.g., hypotension, acute renal, respiratory, and heart failure) in the context of FN is approximately 25% to 30%, and the mortality rate ranges up to 11%. Fever is a common toxicity associated with immune effector cell (IEC) therapy and may be indicative of an infectious process, cytokine release syndrome, or both. Patients receiving this therapy who present with fever (Tmax ≥100.4° F) and concomitant neutropenia (absolute neutrophil count ≤500 cells/mm3) must be treated according to standard FN guidelines. However, fever in this population can at times be stable and otherwise asymptomatic and therefore, may warrant consideration of outpatient FN management. Several tools exist and have been validated to help determine whether oncology patients are at a low or high risk for medical complications as a result of an FN episode and are recommended for use in determining which patients are candidates for inpatient or outpatient FN treatment.

Conditions/situations that are considered a contraindication to the outpatient management of FN and are therefore not eligible to be treated according to this guideline include:

- Poor pulmonary function (FEV1/DLCO <50%, need for O2, COPD)
- Mucositis
- Known specific, active infection such as pneumonia or central line-associated bloodstream infection
- Concern for infection with a resistant organism (ESBL, MRSA, VRE)

Of note, IEC patients who are **non-neutropenic** and experience fever may also be treated according to this guideline per clinician discretion.

Risk Assessment:

The risk index table[1] below has been established by the Vanderbilt Ingram Cancer Center Immune Effector-Cell Committee to identify patients who are candidates for outpatient management of FN based on their potential risk for medical complications.

Modified Neutropenic Fever Symptom Burden (NFSB) score

Characteristic	Score
Fever < 102°F	2
Fever ≥ 102°F	5
New or progressive symptoms based on ROS	5
Hypotension (systolic blood pressure ≤ 90mmHg or mean arterial pressure ≤ 65 mmHG **AND** blood pressure/MAP within 80% of baseline value)	5
Hypoxia (0^2 < 90%)	5
Age > 65 years	2
Dehydration (IVF in last 24 hours)	3
Recent infection or antifungal prescription	4

NOTE: Maximum score is 29; Scoring is cumulative

Decision Tree:
<5 points = Outpatient Management
5-7 points = Admit to observation
≥8 = Admit to inpatient

1. Risk index table will be reviewed for purposes of validation after 5 patients have been assessed utilizing this scoring tool.

Treatment:
If the patient is deemed a potential candidate for outpatient treatment of FN, the following steps should be followed:

1. The patient should present to VUMC for evaluation (clinic or emergency department, if after hours) within 1 hour of identification of fever.
    - Draw appropriate cultures (blood/urine)
    - Administer the first dose of IV broad-spectrum β-lactam antibiotic (cefepime or piperacillin-tazobactam as outlined in VUMC Empiric Anti-Infective Algorithm for Febrile Neutropenia)
    - Obtain standard radiographic imaging (chest X-Ray) as outlined in VUMC Empiric Anti-Infective Algorithm for Febrile Neutropenia
2. .
    - The clinic APP or inpatient nocturnist will then determine, with consultation from the SCT and/or IEC attending, if needed, if the patient is eligible for outpatient management (score ≥21 and no other contraindications)
3. If eligible, the patient should begin usual FN treatment (cefepime, piperacillin-tazobactam) via home infusion
    a) If home infusion or next clinic administration time will be delayed past when the next dose of IV antibiotics is due, the patient may begin an ORAL empiric antibiotic regimen with amoxicillin/clavulanate 1 g PO q12h (or clindamycin 600 mg PO q8h in case of penicillin allergy) and continue prophylactic levofloxacin until IV therapy is secured
        i. All patients will be given a 48-hour supply of amoxicillin/clavulanate or clindamycin along with all other IEC medications on the first day of lymphodepleting chemotherapy to use for this purpose
4. The patient must be seen daily by a health care provider and have daily CBC with differential monitoring while receiving outpatient FN treatment
5. For 72 hours following the onset of the febrile episode and initiation of outpatient FN management, the patient will be physically seen by a provider at the daily 1630 visit/lab check
6. Patients initially managed as outpatients for FN should be evaluated for admission if any of the following occur:
    a) Failure to defervesce after 24-48 hours of empiric antibiotic treatment

b) New or progressive signs/symptoms of infection (not attributable to other causes), including concomitant CRS and/or ICANS

References:

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3. VUMC Empiric Anti-Infective Algorithm for Febrile Neutropenia. https://prd-medweb-cdn.s3.amazonaws.com/documents/vasp/files/FN%20Algorithm%208_18.pdf

Appendix E

Detailed Statistical Considerations

This is an open label, pilot clinical trial to evaluate the feasibility of safely delivering Axi-cel therapy in the outpatient setting. The primary objective of this study is to collect data on a sample of 20 patients to provide data with which to plan a larger, more definitive trial. Sample size was chosen to complete accrual in 24 months.

With 20 observations, categorical variables will be measured with a precision (1/2 of a 95% confidence interval) no larger than 20%. Similarly, the precision of measurement for continuous variables will be proportional to 0.447 standard deviations.

Endpoints

Many endpoints will be measures including patient characteristics, response to therapy by RECIST 1.0 criteria, progression-free (PFS) and overall (OS) survival. PFS is defined as the time from start of therapy to disease progression or death for any reason. OS is defined as the time from start of therapy to death for any reason. Patients progression-free and alive (PFS) or alive (OS) at last follow-up will be censored. The distributions of PFS and OS will be estimated using the Kaplan-Meier (product limit) method. Adverse events according to ASTCT guidelines and CTCAE 5.0 criteria.[1] Feasibility metrics include the proportion of planned doses delivered, 14-day incidence of hospitalization by type and overall, and the proportion of patients that were managed successfully via telemedicine (see above for more details) for more than 3 days post infusion. 95% confidence intervals will be estimated for all endpoints.

General Analysis Plan

Data analysis will be descriptive. No group comparisons will be made. Continuous variable will be summarized using the minimum value, maximum value, 25^{th}, 50^{th} (median), and 75^{th} percentiles as well as the mean and standard deviation. Categorical variables will be summarized in frequency tables.

Continuous Monitoring of Two Important Toxicities

We will carefully monitor two toxicities, CRS and neurotoxicity. Toxicity rates from published data for these events are 15% and 30% respectively. Toxicity will be monitored simultaneously and independently in 20 patients using the Bayesian approach of Thall, Simon, Estey (1995, 1996) as extended by Thall and Sung (1998). [2-4] The probabilities of toxicity for the historical data for these two events are modeled by beta distributions (*Beta*(0.3, 1.7) and *Beta*(0.6, 1.4), respectively), representing 15% and 30% toxicity for an effective sample size of 2 patients. The prior probabilities of toxicity for the experimental regimen are also modeled by beta distributions the same *means* as the corresponding beta distributions for the historical data, also with an effective sample size of 2 patients

Neurotoxicty. Denoting the historical probabilities of toxicity for each endpoint by {p(OR,H) , p(TOX,H)}, the following decision criteria will be applied. Stop if Prob{p(Neurotoxicity,H) < p(Neurotoxicity,E)| data} > 0.75 provides the following monitoring rule,

	Stop the trial if there are this many toxicities total:
# Patients	# Toxicities
1-5	Never stop with this many patients
6-7	4-7
8-9	5-9
10-11	6-11
12-13	7-13
14-15	8-15
16-17	9-17
18-19	10-19
20	Always stop with this many patients

The monitoring rule becomes effective when 6 patients have been treated. If the true neurotoxicity rate is 30%, this rule stops early 17% of the time. For a 50% event rate, this rule stops 70% of the time.

CRS. Denoting the historical probabilities of toxicity for each endpoint by {p(OR,H) , p(TOX,H)}, the following decision criteria will be applied. Stop if Prob{p(CRS,H) < p(CRS,E)| data} > 0.79 provides the following monitoring rule,

	Stop the trial if there are this many toxicities total:
# Patients	# Toxicities
1-5	Never stop with this many patients
6-9	3-9
10-13	4-13
14-17	5-17
18-19	6-19
20	Always stop with this many patients

This is for the event where 15% toxicity it expected and acceptable. If the true toxicity is 15%, this rule stops the trial early 18% of the time. If the true toxicity is 30%, this rule stops the study early (i.e., by an accrual of 19 patients) 69% of the time.

References

1. Lee DW, Santomasso BD, Locke FL, Ghobadi A, Turtle CJ, Brudno JN *et al.* ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells. *Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation* 2019; **25**(4)**:** 625-638. e-pub ahead of print 2018/12/29; doi: 10.1016/j.bbmt.2018.12.758

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Appendix F

PROMIS-29 Profile v2.1

Please respond to each question or statement by marking one box per row.

	Physical Function	**Without any difficulty**	**With a little difficulty**	**With some difficulty**	**With much difficulty**	**Unable to do**
PFA11	Are you able to do chores such as vacuuming or yard work?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA21	Are you able to go up and down stairs at a normal pace?.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA23	Are you able to go for a walk of at least 15 minutes?.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA53	Are you able to run errands and shop?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
	Anxiety **In the past 7 days…**	**Never**	**Rarely**	**Sometimes**	**Often**	**Always**
EDANX01	I felt fearful	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX40	I found it hard to focus on anything other than my anxiety	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX41	My worries overwhelmed me	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX53	I felt uneasy	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
	Depression **In the past 7 days...**	**Never**	**Rarely**	**Sometimes**	**Often**	**Always**
EDDEP04	I felt worthless	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP06	I felt helpless.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP29	I felt depressed.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP41	I felt hopeless.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
	Fatigue **During the past 7 days…**	**Not at all**	**A little bit**	**Somewhat**	**Quite a bit**	**Very much**
HI7	I feel fatigued	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
AN3	I have trouble starting things because I am tired.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

PROMIS–29 Profile v2.1

Fatigue

	In the past 7 days…	Not at all	A little bit	Somewhat	Quite a bit	Very much
FATEXP41	How run-down did you feel on average? ...	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATEXP40	How fatigued were you on average?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Sleep Disturbance

	In the past 7 days…	Very poor	Poor	Fair	Good	Very good
Sleep109	My sleep quality was.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

	In the past 7 days…	Not at all	A little bit	Somewhat	Quite a bit	Very much
Sleep116	My sleep was refreshing.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Sleep20	I had a problem with my sleep	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Sleep44	I had difficulty falling asleep	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Ability to Participate in Social Roles and Activities

		Never	Rarely	Sometimes	Usually	Always
SRPPER11_CaPS	I have trouble doing all of my regular leisure activities with others.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
SRPPER18_CaPS	I have trouble doing all of the family activities that I want to do	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
SRPPER23_CaPS	I have trouble doing all of my usual work (include work at home)	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
SRPPER46_CaPS	I have trouble doing all of the activities with friends that I want to do	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

Pain Interference

	In the past 7 days…	Not at all	A little bit	Somewhat	Quite a bit	Very much
PAININ9	How much did pain interfere with your day to day activities?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAININ22	How much did pain interfere with work around the home?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAININ31	How much did pain interfere with your ability to participate in social activities? .	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAININ34	How much did pain interfere with your household chores?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Pain Intensity

In the past 7 days…

Global07	How would you rate your pain on average?.....	☐ 0 No pain	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10 Worst pain imaginable

Appendix G: Biofourmis Wearable Device

Introduction

Subjects undergoing CART therapy are admitted to the hospital for 7 days or longer for close monitoring. During that time, the close monitoring consists of physical exam up to four times (One by physician, one by NP, twice by nurses) and vitals are measured at least six times (every 4 hours x 24 hours).
Biofourmis has FDA/IDE certified wearable devices that are already in use in the clinical setting This project explores how wearable devices might be of use in the research setting to enhance the close monitoring of patients and bridge the gap between the impatient and outpatient setting Data are collected for research purposes only.

Data captured

Body surface temperature, Respiratory rate, Heart rate, Blood Pressure, Oxygen saturation

Devices

1. Seven-day patch to be worn on the left anterior chest
2. Blood Pressure cuff to be worn on the arm intermittently
3. Pulse oximeter device to be worn on the digits intermittently

Device Clearances: BP cuff and pulse oximeter are FDA approved while the patch is IDE approved

Methods

Subjects are trained to apply the devices which comprises of a patch that is applied on the left anterior chest and worn continuously, a blood pressure cuff that is applied intermittently on the arm, and a pulse oximeter applied intermittently to the digits. The BP cuff and pulse oximeter are applied at specific times (6am, 12 noon, 16:30 +/- 1 hour and 22:00) while the patch captures heart rate, temperature, and respiratory rate continuously. If patient fails to apply the BP cuff and pulse oximeter at the time stipulated, a vendor system generated reminder will go to them. Any alerts issued by vendor can be viewed by the PI and all authorized users of the program. Data are recorded in the device database and are for research only but are accessible by specific clinical trial staff.
Between day -5 and day zero: Subjects are taught to apply and use devices
Day zero: Subjects are given the devices and begin to wear them
Day zero through day +14: Subjects use the devices as directed
Day 14 – 21: Devices are returned to the vendor

Data management

This is an exploratory objective. We will track the frequency of abnormal vital signs, any alarms generated by system and time to resolution of the alarms. Data collected will be analyzed post hoc using machine learning to evaluate for any predictive pattern for hospitalization and other outcomes.