Official Title of Study:

A Phase 2 Study of Lisocabtagene Maraleucel (JCAR017) as Second-Line Therapy in Adult Patients with Aggressive B-cell NHL (TRANSCEND-PILOT-017006)

PROTOCOL: 17006

NCT Number: NCT03483103

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A PHASE 2 STUDY OF LISOCABTAGENE MARALEUCEL (JCAR017) AS SECOND-LINE THERAPY IN ADULT PATIENTS WITH AGGRESSIVE B-CELL NHL (TRANSCEND-PILOT-017006)

Protocol Number:	**017006 Amendment 6**
Study ID:	TRANSCEND-NHL-006
NCT Number:	03483103
IND Number	016506
Date:	16 Aug 2021
Regulatory Sponsor:	Juno Therapeutics, Inc. A wholly owned subsidiary of Celgene Corporation 400 Dexter Ave North Suite 1200 Seattle, WA 98109 Phone: 206-582-1600 www.junotherapeutics.com
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Safety Reporting:	[redacted]

This trial will be conducted in compliance with the protocol, International Council for Harmonisation Good Clinical Practice (ICH GCP), and applicable state, local, and federal regulatory requirements.

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CELGENE THERAPEUTIC AREA HEAD SIGNATURE PAGE

{See appended electronic signature page}	
Signature of Celgene Therapeutic Area Head	**dd mmm yyyy**
[redacted]	
Printed Name of Celgene Therapeutic Area Head and Title	
By my signature, I indicate I have reviewed this summary of changes and find its content to be acceptable.	

SITE PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Signature of Site Principal Investigator	**dd mmm yyyy**
Printed Name of Site Principal Investigator **Institution Name:**_____ By my signature, I agree to personally supervise the conduct of this study at my study site and to ensure its conduct is in compliance with the protocol, informed consent, Institutional Review Board (IRB)/Ethics Committee (EC) procedures, instructions from Celgene representatives, the Declaration of Helsinki, International Council for Harmonisation (ICH) Good Clinical Practices Guidelines, and local regulations governing the conduct of clinical studies.	

PROTOCOL SYNOPSIS

Protocol Number: 017006

Protocol Title: A Phase 2 study of Lisocabtagene Maraleucel (JCAR017) as Second-Line Therapy in Adult Patients with Aggressive B-cell NHL (TRANSCEND-PILOT-017006)

Sponsor: Juno Therapeutics, Inc., a wholly owned subsidiary of Celgene Corporation

Study Rationale:
Outcomes are poor and additional options are needed for patients who have failed front-line therapy and are not eligible for hematopoietic stem cell transplantation (HSCT). Data from Juno Study 017001 demonstrate that treatment with JCAR017 in subjects with aggressive B-cell non-Hodgkin lymphoma (NHL) who have failed 2 or more lines of therapy results in encouraging efficacy outcomes and has an acceptable safety profile. The purpose of this study is to evaluate the use of JCAR017 in subjects who have failed one previous line of therapy for aggressive B-cell NHL and are not eligible for HSCT.

Study Objectives:
Primary:

- To assess the antitumor activity (overall response rate, ORR) of JCAR017 in adult subjects with aggressive B-cell NHL who are ineligible for HSCT

Secondary:

- To evaluate the safety of JCAR017
- To assess the complete response (CR) rate and durability of antitumor activity of JCAR017
- To estimate the progression-free survival (PFS), event-free survival (EFS), and overall survival (OS) of subjects treated with JCAR017
- To characterize the pharmacokinetic (PK) profile of JCAR017 in this subject population
- To assess health-related quality of life (HRQoL) and health economics and outcomes research (HEOR)

Exploratory:

- To assess immune responses to JCAR017
- To assess the pharmacodynamic effects of JCAR017
- To assess CAR T subset expansion and persistence
- To assess the effect of JCAR017 attributes on safety, PK, and antitumor activity
- To assess the effect of tumor and tumor microenvironment on JCAR017 PK and clinical response

Study Design:
This is an open-label, multicenter, Phase 2 study to determine the antitumor activity, PK, and safety of JCAR017 in subjects who have relapsed from, or are refractory to, a single line of immunochemotherapy for aggressive B-cell NHL and are ineligible for HSCT (as defined in the eligibility criteria). Subjects will be treated with lymphodepleting chemotherapy and JCAR017.

Upon enrollment, subjects will undergo leukapheresis to enable JCAR017 product generation. A baseline tumor biopsy (either a historical sample, or if not available, a fresh tumor sample) will be obtained. While JCAR017 is being manufactured, if required to control disease, subjects may receive salvage low-dose chemotherapy or one cycle of non-curative standard of care antitumor therapy.

Upon successful JCAR017 product generation, subjects will enter the treatment phase. Treatment includes lymphodepleting chemotherapy with fludarabine and cyclophosphamide (flu/cy) followed by JCAR017 at a dose of 100×10^6 CAR+ T cells administered intravenously (IV) 2 to 7 days after completion of lymphodepleting chemotherapy.

If a subject has achieved a CR to JCAR017 and subsequently progressed, they may receive retreatment only if doses are available and remanufacturing is not required. Details regarding retreatment are provided in the protocol.

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After treatment with JCAR017, subjects will enter post-treatment follow-up, and will be followed on this study for 2 years for safety, PK and biomarkers, disease status, HRQoL, and survival, as described in more detail in the assessments sections below. Assessments for long-term safety, overall survival, and HRQoL will continue even after disease progression. After completion of 2 years of assessments in this protocol, long-term follow-up (LTFU) for survival, long-term toxicity, and viral vector safety will continue under a separate protocol for up to 15 years after JCAR017 treatment.

Toxicity will be evaluated on an ongoing basis by the Sponsor and reviewed at regularly scheduled Investigator Safety calls. Additionally, safety monitoring boundaries based on the incidence of Grade 3 or above, JCAR017-related, treatment-emergent neurological toxicity and prolonged Grade 4 and Grade 5 individual safety events will be established using a Bayesian framework as described in "Safety Assessments," below.

Oversight Committees:

Data Safety Monitoring Board:
An independent Data Safety Monitoring Board (DSMB) will review cumulative study data approximately semiannually over the course of the study to evaluate safety, protocol conduct, and scientific validity and integrity of the trial.

Independent Review Committee:
An Independent Review Committee (IRC) will be established to determine response and progression status.

Study Population:
The target study population consists of subjects with aggressive B-cell NHL who have failed front-line chemoimmunotherapy.

Inclusion Criteria:
Subjects must meet all the following criteria to be enrolled in this study:

1. Age ≥ 18 years at the time of consent
2. Signed written informed consent obtained prior to any study procedures
3. Confirmation of relapsed or refractory (R/R) aggressive B-cell NHL of the following histologies at relapse:
   a. Diffuse large B-cell lymphoma (DLBCL), not otherwise specified (NOS; de novo or transformed follicular lymphoma [tFL]), high-grade B-cell lymphoma (HGL) with MYC and BCL2 and/or BCL6 rearrangements with DLBCL histology (double/triple hit lymphoma [DHL/THL]) or
   b. Follicular lymphoma Grade 3B (FL3B) per WHO 2016 classification
4. Previous treatment must include:
   a. Treatment for a qualifying histology (as defined in inclusion criterion 3 above) with a single line of chemoimmunotherapy containing an anthracycline and a CD20-targeted agent, such as rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP)
5. Subjects must be deemed ineligible for both high-dose chemotherapy and HSCT while also having adequate organ function for CAR T cell treatment. To be eligible for this study, subjects must meet **at least ONE** transplant ineligible (TNE) criterion as defined below:
   a. TNE criteria (must meet **at least ONE**):
      (1) Age ≥ 70 years
      (2) Eastern Cooperative Oncology Group (ECOG) performance status = 2
      (3) Impaired pulmonary function: diffusing capacity of the lung for carbon monoxide (DLCO) ≤ 60% adjusted for gender-specific hemoglobin concentration
      (4) Impaired cardiac function: left ventricular ejection fraction (LVEF) < 50%; must be assessed by echocardiogram or multiple uptake gated acquisition (MUGA) scan performed within 4 weeks of determination of eligibility
      (5) Impaired renal function: calculated creatinine clearance (Cockcroft and Gault) < 60 mL/min
      (6) Impaired hepatic function: aspartate aminotransferase (AST)/alanine aminotransferase (ALT) > 2 × upper limit of normal (ULN)
   b. Adequate organ function criteria (must meet **all**):

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(1) SaO2 ≥ 92% on room air AND Common Terminology Criteria for Adverse Events (CTCAE) ≤ 1 dyspnea
(2) LVEF ≥ 40%
(3) Calculated creatinine clearance (Cockcroft and Gault) > 30 mL/min
(4) AST/ALT ≤ 5 × ULN
(5) Assessed by the Investigator to have adequate bone marrow function to receive lymphodepleting chemotherapy
(6) Total bilirubin < 2.0 mg/dL (or < 3.0 mg/dL for subjects with Gilbert's syndrome or lymphomatous infiltration of the liver)

6. Positron emission tomography (PET)-positive disease according to the "Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification"
7. Histological confirmation of diagnosis at last relapse. Enough tumor material must be available for central confirmation of diagnosis, otherwise a new tumor biopsy is mandated. NOTE: if subsequent therapies are given after last relapse with SD/PD as best response, the tissue from that last relapse will be considered adequate to participate in the trial.
8. ECOG performance status of 0, 1, or 2
9. Adequate vascular access for leukapheresis procedure (either peripheral line or surgically-placed line)
10. Females of childbearing potential (FCBP*) subjects must:
    a. Either commit to true abstinence** from heterosexual contact (which must be reviewed on a monthly basis and source documented) or agree to use, and be able to comply with, effective contraception without interruption. Contraception methods must include 1 highly effective method from screening until at least 12 months after the lymphodepleting chemotherapy.
    b. Agree to abstain from breastfeeding during study participation and for at least 12 months following lymphodepleting chemotherapy.
    c. There are insufficient exposure data to provide any recommendation concerning the duration of contraception and the abstaining from breastfeeding following treatment with JCAR017. Any decision regarding contraception and breastfeeding after JCAR017 infusion should be discussed with the treating physician.

       Note: Highly effective methods are defined as those that result in a low failure rate (ie, less than 1% per year) when used consistently and correctly. The following are examples of highly effective and additional effective methods of contraception:

       - Intrauterine device (IUD)
       - Hormonal (birth control pill, injections, implants)
       - Tubal ligation
       - Partner's vasectomy
11. Females of childbearing potential (FCBP*) subjects must have 2 negative pregnancy tests as verified by the Investigator (one negative serum beta-human chorionic gonadotropin [ß-hCG] pregnancy test result at screening, and within 7 days prior to the first dose of lymphodepleting chemotherapy). This applies even if the subject practices true abstinence** from heterosexual contact.
12. Male subjects must:
    a. Practice true abstinence** (which must be reviewed on a monthly basis) or agree to use a condom during sexual contact with a pregnant female or a female of childbearing potential for 12 months after lymphodepleting chemotherapy even if he has undergone a successful vasectomy.
    b. There are insufficient exposure data to provide any recommendation concerning the duration of contraception following treatment with JCAR017. Any decision regarding contraception after JCAR017 infusion should be discussed with the treating physician.

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* A female subject of childbearing potential (FCBP) is a female who: 1) has achieved menarche at some point, 2) has not undergone a hysterectomy or bilateral oophorectomy or 3) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 12 consecutive months (ie, has had menses at any time in the preceding 12 consecutive months).

** True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. In contrast, periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

13. Subjects must agree to not donate blood, organs, sperm or semen, and egg cells for usage in other individuals for at least 1 year following lymphodepletion chemotherapy. There are insufficient exposure data to provide any recommendation concerning the duration of refraining from tissue donation following treatment with JCAR017. Therefore, subjects treated with JCAR017 should not donate blood, organs, tissues, and cells for transplantation

Exclusion Criteria:
Subjects who meet any of the following criteria will be excluded from participation in this study:

1. Subjects with central nervous system (CNS)-only involvement by malignancy (note: subjects with secondary CNS involvement are allowed on study)
2. History of another primary malignancy that has not been in remission for at least 2 years. The following are examples of exemptions from the 2-year limit: nonmelanoma skin cancer, definitively treated stage 1 solid tumor with low risk for recurrence, curatively treated localized prostate cancer, and cervical carcinoma in situ on biopsy or a squamous intraepithelial lesion on PAP smear.
3. Previous treatment with CD19-targeted therapy, except prior JCAR017 treatment in this protocol for subjects receiving retreatment
4. Treatment with alemtuzumab within 6 months of leukapheresis, or treatment with fludarabine or cladribine within 3 months of leukapheresis
5. Active hepatitis B or active hepatitis C infection. (Subjects with a negative polymerase chain reaction [PCR] assay for viral load for hepatitis B or C are permitted; subjects positive for hepatitis B surface antigen [HBsAg] and/or anti-hepatitis B core antibody [HBcAb] with negative viral load are eligible and should be considered for prophylactic antiviral therapy)
6. History of or active human immunodeficiency virus (HIV) infection at the time of screening
7. Subjects with uncontrolled systemic fungal, bacterial, viral or other infection despite appropriate antibiotics or other treatment at the time of leukapheresis or JCAR017 administration
8. History of any one of the following cardiovascular conditions within the past 6 months: Class III or IV heart failure as defined by the New York Heart Association (NYHA), cardiac angioplasty or stenting, myocardial infarction, unstable angina, or other clinically significant cardiac disease
9. History or presence of clinically relevant CNS pathology such as epilepsy, seizure, aphasia, stroke, severe brain injuries, dementia, Parkinson's disease, cerebellar disease, cerebral edema, organic brain syndrome, or psychosis
10. Pregnant or nursing (lactating) females; subjects must agree to abstain from breastfeeding during study participation and for at least 1 year following lymphodepleting chemotherapy
11. Use of the following:
    - Therapeutic doses of corticosteroids (defined as > 20 mg/day prednisone or equivalent) within 7 days prior to leukapheresis or 72 hours prior to JCAR017 administration. Physiologic replacement, topical, and inhaled steroids are permitted.
    - Cytotoxic chemotherapeutic agents that are not considered lymphotoxic (eg, doxorubicin, vincristine, gemcitabine, oxaliplatin, carboplatin, etoposide) within 1 week of leukapheresis. Oral chemotherapeutic agents, including lenalidomide and ibrutinib, are allowed if at least 3 half-lives have elapsed prior to leukapheresis.
    - Lymphotoxic chemotherapeutic agents (eg, cyclophosphamide, ifosfamide, bendamustine, melphalan) within 2 weeks of leukapheresis

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- Experimental agents within 4 weeks of leukapheresis unless no response or disease progression is documented on the experimental therapy and at least 3 half-lives have elapsed prior to leukapheresis
- Radiation within 6 weeks of leukapheresis. Subjects must have progressive disease in irradiated lesions or have additional non-irradiated, PET-positive lesions to be eligible. Radiation to a single lesion, if additional non-irradiated PET-positive lesions are present, is allowed up to 2 weeks prior to leukapheresis.

12. Prior hematopoietic stem cell transplant
13. Uncontrolled medical, psychological, familial, sociological, or geographical conditions that do not permit compliance with the protocol, as judged by the Investigator; or unwillingness or inability to follow the procedures required in the protocol
14. Progressive vascular tumor invasion, thrombosis, or embolism
15. Venous thrombosis or embolism not managed on a stable regimen of anticoagulation

Investigational Product, Dose, and Mode of Administration:
The JCAR017 investigational drug product is comprised of autologous CD8+ and CD4+ T cells that express a CD19-specific chimeric antigen receptor (CAR) that are provided as frozen cell suspensions for IV administration. The JCAR017 investigational drug product is provided as 2 individually formulated CD8+ and CD4+ T cell suspensions in media containing dimethyl sulfoxide (DMSO) for direct IV administration in equal CAR T-cell quantities into the subject.

JCAR017 at a dose of 100×10^6 CAR+ T cells (50×10^6 CD8+ CAR+ T cells and 50×10^6 CD4+ CAR+ T cells), will be given IV in a single-dose schedule on Day 1 (between 2 and 7 days following the completion of lymphodepleting chemotherapy) of a 28-day cycle. If a subject has achieved a CR to JCAR017 and subsequently progressed, they may receive retreatment only if doses are available and remanufacturing is not required.

Duration of Study and Subject Participation:
The duration of study for each subject is approximately 2 years, and the estimated total time from first subject first visit for all subjects to complete the study is approximately 4 years.

Efficacy Assessments:
Treatment response will be assessed at approximately Day 29 and Months 3, 6, 9, 12, 18, and 24. Assessment will occur via radiographic tumor evaluation by diagnostic quality CT scans (chest, neck, abdomen, and pelvis) and PET scans. Assessment of bone marrow involvement by lymphoma will be by PET scan only; bone marrow aspirates and biopsies will not be required for assessment of disease response. Disease response will be determined according to the "Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification," as well as other pertinent clinical data as appropriate. For subjects with suspected or confirmed CNS involvement, repeat cerebrospinal fluid (CSF) assessments by flow cytometry will be performed.

Safety Assessments:
AEs/SAEs and laboratory abnormalities (type, frequency, and severity) will be collected. AESIs may include but are not limited to infusion reaction, prolonged cytopenia, cytokine release syndrome (CRS), neurological toxicity, macrophage activation syndrome (MAS), tumor lysis syndrome (TLS), Grade ≥ 3 infection, hypogammaglobulinemia, autoimmune disorder, and second primary malignancy. Safety monitoring boundaries based on the incidence of Grade 3 or above, JCAR017-related, treatment-emergent neurological toxicity and prolonged Grade 4 and Grade 5 individual safety events will be established using a Bayesian framework to help detect safety signals during the study. If the safety boundaries are crossed, enrollment will be paused and an ad hoc DSMB meeting will be held to review the data. Enrollment will remain paused pending the DSMB's recommendations.

Pharmacokinetic and Biomarker Assessments:
Samples will be taken for PK and biomarker assessments at specified time points throughout the study. A tumor biopsy (in subjects with accessible disease) will be obtained pretreatment, anytime from Day 8 to 17, and at disease progression. Collection of tissue from latest archived tumor biopsy (block or slides) will be collected. If

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archival sample is before most recent relapse, a new tumor biopsy is mandated to confirm diagnosis for subjects with accessible disease. Assessment of JCAR017 PK will be determined by quantitative PCR (qPCR) to detect the JCAR017 transgene. Flow cytometry analysis will be performed as an exploratory endpoint to characterize the expansion and persistence of CD4+ and CD8+ CAR T cell subsets. Immune responses to JCAR017 will be assessed. Biomarker assessments will include profiling of CAR and endogenous T cells from blood, tumor and tumor microenvironment characterization, enumeration of immune cell subsets, and assessment of cytokines and chemokines associated with CRS, neurological toxicity, and immune cell function. Peripheral blood and lymphoma biopsies will be collected for these evaluations, as well as bone marrow biopsy/aspirate and CSF samples if clinically indicated.
HRQoL and HEOR Assessments: Quality-of-life outcomes will be assessed using the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30, the FACT-Lym subscale, and the EuroQol instrument EQ-5D-5L, which will be collected at specified time points throughout the study. Information on hospitalizations will be collected throughout the study and used to assess health economics and outcomes.
Statistical Methods: AEs/SAEs, AESIs, laboratory abnormalities, and PK information will be described and summarized based on the JCAR017-treated Analysis Set. Results will be presented using descriptive statistics. Efficacy information will be summarized. A primary efficacy analysis of ORR will be based on the JCAR017-treated Efficacy Analysis Set using IRC assessments of disease status. This primary efficacy analysis will test the null hypothesis of ORR $\leq$ p0% against the alternative hypothesis that the ORR > p0% at a 1-sided 0.025 level of significance. A retrospective patient-level real-world cohort is being planned to generate a comparable external/synthetic control, which will be used to provide a null hypothesis p0% for testing the primary endpoint of ORR. The final analyses will be carried out after all subjects have completed or discontinued the study due to any reason. No formal hypothesis testing will be performed at the final analysis. **Justification for Sample Size:** A sample size of approximately 62 subjects in the JCAR017-treated Efficacy Analysis Set provides at least 85% power to reject the null hypothesis of overall response rate less than 50% assuming the target response rate of 70% using an exact binomial test with 1-sided significance level 0.025. The assumption of the null hypothesis of 50% ORR used to size the study is supported by the results of a meta-analysis of available literature across 12 studies of subjects receiving second-line treatment. EAST v6.4.1 is used to calculate the sample size and power.

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LIST OF ABBREVIATIONS

Abbreviation or Term	Definition/Explanation
aaIPI	age-adjusted International Prognostic Index
AE	adverse event
AESI	adverse event of special interest
ALC	absolute lymphocyte count
ALL	acute lymphoblastic leukemia
Allo-HSCT	allogeneic hematopoietic stem cell transplant
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
ASTCT	American Society for Transplantation and Cellular Therapy
ATA	anti-therapeutic antibody
AUC	area under the curve
ß-hCG	beta-human chorionic gonadotropin
BMA	bone marrow aspirate
BMB	bone marrow biopsy
BUN	blood urea nitrogen
CAR	chimeric antigen receptor
CBC	complete blood count
CFR	Code of Federal Regulations
CLL	chronic lymphocytic leukemia
Cmax	maximum concentration
CNS	central nervous system
CR	complete response
CRA	clinical research associate
CRF	case report form
CRP	C-reactive protein
CRS	cytokine release syndrome
CSF	cerebrospinal fluid
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DHL/THL	double hit lymphoma/triple hit lymphoma
DLBCL	diffuse large B-cell lymphoma

Abbreviation or Term	Definition/Explanation
DLCO	diffusing capacity of the lung for carbon monoxide
DLI	donor lymphocyte infusions
DMSO	dimethyl sulfoxide
DOR	duration of response
DSMB	Data Safety Monitoring Board
EC	Ethics Committee
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data capture
EEG	electroencephalogram
eGFR	estimated glomerular filtration rate
EGFRt	truncated human epidermal growth factor receptor
EOS	End-of-Study
FDA	Food and Drug Administration
FISH	fluorescence in situ hybridization
FL3B	follicular lymphoma grade 3B
flu/cy	fludarabine and cyclophosphamide
GCB	germinal center B-cell
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GM-CSF	granulocyte macrophage colony-stimulating factor
GVHD	graft versus host disease
HBsAg	anti-hepatitis B surface antigen
HBcAb	anti-hepatitis B core antibody
HCT-CI	hematopoietic cell transplant specific comorbidity index
HEOR	health economics and outcomes research
HGL	high-grade B-cell lymphoma
HIV	human immunodeficiency virus
HRQoL	health-related quality of life
HSCT	hematopoietic stem cell transplant
IB	Investigator's brochure
IBC	Institutional Biosafety Committee
ICE	Immune Effector Cell-Associated Encephalopathy

Abbreviation or Term	Definition/Explanation
ICF	informed consent form
ICH	International Council on Harmonisation
ICMJE	International Committee of Medical Journal Editors
ICU	intensive care unit
IFNγ	interferon gamma
IgA, G, or M	Immunoglobulin A, G, or M
IgH	immunoglobulin heavy chain
IL-5, 6, or 10	Interleukin-5, 6, or 10
IPI	International Prognostic Index
IRB	Institutional Review Board
IRC	Independent Review Committee
IV	intravenous
KM	Kaplan-Meier
LDC	lymphodepleting chemotherapy
LDH	lactate dehydrogenase
LN2	liquid nitrogen
LTFU	long-term follow-up
LVEF	left ventricular ejection fraction
mAb	monoclonal antibody
MAS	macrophage activation syndrome
MCL	mantle cell lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
MMSE	Mini Mental State Examination
MRI	magnetic resonance imaging
MUGA	multiple uptake gated acquisition
NCI	National Cancer Institute
NHL	non-Hodgkin lymphoma
NIH	National Institutes of Health
NK	natural killer
NOS	not otherwise specified
NT	neurologic toxicities
NYHA	New York Heart Association
OR	objective response
ORR	overall response rate

Abbreviation or Term	Definition/Explanation
OS	overall survival
PBMC	peripheral blood mononuclear cell
PCP	Pneumocystis pneumonia
PCR	polymerase chain reaction
PD	progressive disease
PET	positron emission tomography
PFS	progression-free survival
PJP	pneumocystis pneumonia
PK	pharmacokinetic(s)
PMBCL	primary mediastinal B-cell lymphoma
PO	per os (orally)
PPDP	Protocol Product Deviation Plan
PRO	patient-reported outcome
qPCR	quantitative polymerase chain reaction
R-CHOP	rituximab with cyclophosphamide, doxorubicin, vincristine, and prednisone
RCL	replication-competent lentivirus
R/R	relapsed or refractory
SAE	serious adverse event
SAP	Statistical Analysis Plan
SaO_2	saturated oxygen
sCD25	soluble IL2 receptor
scFv	single chain variable fragment
SCID	severe combined immunodeficiency
sCRS	severe cytokine release syndrome
SD	stable disease
SIN	self-inactivating
SNP	single nucleotide polymorphism
SOC	system organ class
SPD	sum of the product of the perpendicular diameters
SPM	second primary malignancy
tDLBCL	transformed DLBCL from indolent histology
TEAE	treatment-emergent adverse event
TLS	tumor lysis syndrome
TMG	Toxicity management guidelines

Abbreviation or Term	Definition/Explanation
TNE	transplant ineligible
TNF-α	Tumor necrosis factor alpha
ULN	upper limit of normal
USPI	United States Product Insert

1. INTRODUCTION

1.1. B-cell Non-Hodgkin Lymphoma

It is estimated that approximately 72,000 new cases of non-Hodgkin lymphoma (NHL) will be diagnosed and approximately 20,000 patients will die of their disease in the United States in 2019 (Siegel 2019). NHL is the seventh most common cancer in the US, accounting for 4.2% of new cancers and 3.3% of all cancer-related deaths (SEER 2019). In the US, about 80 to 85% of NHL cases are categorized as B-cell lymphomas and 15 to 20% are categorized as T/natural killer (NK)-cell lymphomas (NCCN 2019). The most common types of aggressive B-cell NHL are diffuse large B cell lymphoma (DLBCL) and mantle cell lymphoma (MCL). With current treatments, relapsed or refractory (R/R) aggressive B-cell NHL has poor outcomes, and the efficacy of salvage options are diminished in the era of rituximab-containing regimens (Wilson 2013). As such, there remains a need to develop new therapies for R/R B-cell NHL.

Historically, first-line treatment for patients with high-stage aggressive B-cell NHL, including DLBCL, primary mediastinal B-cell lymphoma (PMBCL), and follicular lymphoma Grade 3B, has been six or eight cycles of rituximab with cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP), with reduced-intensity dosing regimens recommended for the infirm or very elderly population > 80 years of age (NCCN 2019). Recently, data have been reported that support more intensive therapy for PMBCL in the upfront setting (NCCN 2019), and ongoing studies are evaluating augmented R-CHOP regimens for improvement of outcomes in high-risk subtypes of aggressive B-cell NHL.

Approximately one-third of DLBCL patients will be refractory to or relapse after R-CHOP within five years of diagnosis (Cunningham 2013). Patients at high risk of relapse to R-CHOP include those with a high international prognostic index [IPI] score (Ziepert 2010, Cunningham 2013), activated B-cell [ABC] or non-germinal center B-cell [non-GCB] cell of origin (Fu 2008, Culpin 2013), and double-hit DLBCL, now referred to as high-grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements (Friedberg 2012, Morgan 2013). In these high-risk groups, 50% or less of patients are disease-free at two years (Ziepert 2010, Culpin 2013, Morgan 2013). Overall survival (OS) for all DLBCL patients approaches 75% at five years (Cunningham 2013); however, in high-risk patients, it may be as low as 25%-30% (double-hit and non-GCB) to 50% (IPI 3-5) at five years (Ziepert 2010, Culpin 2013, Morgan 2013).

For those patients who are refractory or relapse following front-line therapy and are eligible for hematopoietic stem cell transplant (HSCT), various high-dose, platinum-based salvage chemotherapy regimens are recommended (NCCN 2019). It is estimated that 35 to 50% of R/R patients are not suitable for high-dose chemotherapy, for reasons including (but not limited to) comorbidities, poor performance status, or age, and thus not eligible for HSCT. These patients may be treated with a platinum and/or gemcitabine-based regimen such as rituximab, gemcitabine and oxaliplatin (R-GemOx), which may be combined with involved-field radiation therapy (El Gnaoui 2007), or preferentially be enrolled in clinical trials testing the activity of novel drugs or combinations of agents. The effectiveness of combination and single agent therapies is limited to a minority of those treated. Recently, the FDA approved Yescarta™ (axicabtagene ciloleucel), an anti-CD19 CAR T cell product, to treat adult patients with DLBCL who have not responded to or who have relapsed after at least two prior lines of therapy.

Therefore, there is significant unmet need for patients who are ineligible for transplant following front-line therapy.

In order to provide a basis for sizing this trial of second-line therapy in this patient population, the Sponsor performed a meta-analysis (based on fixed and random effects models) on data from 12 published studies of second-line therapy recommended by the NCCN guidelines for patients with R/R aggressive large B-cell NHL (Table 1). Of note, the patient population in these studies included a mixture of diagnoses, numbers and types of prior lines of therapies, and patient performance status, and did not exactly match the population to be enrolled in the current study.

This meta-analysis shows an ORR of 46% (95% CI 0.43, 0.50) using the fixed-effect model and 52% (95% CI 0.44, 0.59) using the random-effects model. Additionally, the published median PFS ranged from 3 to 7 months, showing low durability of response. Taken together, these data show a high unmet need in R/R aggressive B-cell NHL patients who are not eligible for HSCT.

A retrospective patient-level real-world data cohort is being planned to generate a comparable external/synthetic control, which will be used to provide a null hypothesis for testing the primary endpoint of ORR. Generation of this external control will be discussed in detail in a separate real-world evidence study Statistical Analysis Plan.

Table 1: Summary of Historical ORR and CR Rates for Second-Line Treatment of R/R Aggressive B-cell NHL

Products Tested [Publication]	Product(s)	N Evalu-able	ORR (%)	CR/Cru (%)	mDOR (mo)	mPFS (mo)	mOS (mo)
Gemcitabine plus oxaliplatin, with rituximab (Corazzelli 2009)	Gemcitabine plus oxaliplatin, with rituximab	32	78	50	N/Av	N/Av	N/Av
Gemcitabine plus oxaliplatin, without rituximab (Corazzelli 2009)	Gemcitabine plus oxaliplatin, without rituximab	30	57	30	N/Av	N/Av	N/Av
Gemcitabine plus oxaliplatin, with rituximab (El Gnaoui 2007)	Gemcitabine plus oxaliplatin, with rituximab	46	83	50	N/Av	N/Av	N/Av
Gemcitabine plus oxaliplatin, with rituximab (Mounier 2013)	Gemcitabine plus oxaliplatin, with rituximab	49	61	44	10	5.3	11
Inotuzumab ozogamicin plus rituximab versus chemotherapy plus rituximab (Dang 2018)	Inotuzumab ozogamicin plus rituximab	166	41	N/Av	11.6	3.7	9.5
Inotuzumab ozogamicin plus rituximab versus chemotherapy plus rituximab (Dang 2018)	Investigator's choice of rituximab plus bendamustine or rituximab plus gemcitabine	172	44	N/Av	6.9	3.5	9.5
Single-agent lenalidomide (Witzig 2011)	Lenalidomide	217	35	13	10.6	3.7	N/Av
Single-agent lenalidomide (Wiernik 2008)	Lenalidomide	49	35	12	6.2	4	N/Av
Lenalidomide plus rituximab (Wang 2013)	Lenalidomide plus rituximab	45	33	N/Av	10.2	3.7	10.7
Bendamustine plus rituximab (Ohmachi 2013)	Bendamustine plus rituximab	59	63	37	N/Av	6.7	N/Av

Table 1: Summary of Historical ORR and CR Rates for Second-Line Treatment of R/R Aggressive B-cell NHL (Continued)

Products Tested [Publication]	Product(s)	N Evalu-able	ORR (%)	CR/Cr (%)	mDOR (mo)	mPFS (mo)	mOS (mo)
Bendamustine plus rituximab (Vacirca 2013)	Bendamustine plus rituximab	48	46	15	17.3	3.6	NR
Clofarabine (Nabhan 2011)	Clofarabine	31	42	23	5	6	10
Gemcitabine, carboplatin, dexamethasone, and rituximab (Gopal 2010)	Gemcitabine, carboplatin, dexamethasone, and rituximab	51	67	31	N/Av	N/Av	N/Av
Gemcitabine, dexamethasone, and cisplatin (Crump 2004)	Gemcitabine, dexamethasone, and cisplatin	51	49	16	N/Av	N/Av	8.9
Meta-analysis, Fixed-effect model			0.46 [0.43; 0.50]	0.27 [0.23; 0.31]			
Meta-analysis, Random-effects model			0.52 [0.44; 0.59]	0.27 [0.19; 0.37]			

CR, complete response; CRu, unconfirmed complete response; mDOR, median duration of response; mo, months; mOS, median overall survival; mPFS, median progression-free survival; N/Av, not available; NR, not reached; ORR, overall response rate; TNE, transplant ineligible.

1.2. CD19 as a Therapeutic Target

CD19 is a 95-kDa glycoprotein present on B-cells from early development until differentiation into plasma cells (Stamenkovic 1988). It is a member of the immunoglobulin superfamily and a component of a B cell surface signal transduction complex that positively regulates signal transduction through the B-cell receptor (Stamenkovic 1988, Brentjens 2011).

CD19 is an attractive therapeutic target because it is expressed by most B-cell malignancies, including B-cell NHL (Li 1993, Li 1996, Davila 2012). Importantly, the CD19 antigen is not expressed on hematopoietic stem cells or on any normal tissue apart from those of the B cell lineage.

1.3. CD19-Targeted Chimeric Antigen Receptors

CD19-specific chimeric antigen receptors (CARs) are single chain variable fragments (scFv) fused to a transmembrane domain and cytoplasmic signaling domains. Expression of the CD19-directed CAR in autologous T cells is achieved by ex vivo transfection using a recombinant retroviral or lentiviral vector. The CAR is expressed on the T cell surface and redirects the transfected T cells to CD19-expressing lymphoma cells, leading to CD19-specific tumor cell recognition, lysis, cytokine secretion and T cell proliferation (Sadelain 2013). In clinical studies, CD19-targeted CARs have demonstrated encouraging activity in adult and pediatric subjects with R/R B cell acute lymphoblastic leukemia (ALL) and B-cell NHL (Turtle 2016a, Gardner 2017, Neelapu 2017, Schuster 2017, Maude 2018, Park 2018). Promising results have been reported for different CD19-directed CARs in the treatment of adult (Turtle 2016b, Neelapu 2017, Schuster 2017) and pediatric (Park 2016) CD19-positive lymphoid malignancies.

Three CD19-directed CAR T therapies have been approved by the US Food and Drug Administration (FDA):

- Tisagenlecleucel, approved for the treatment of patients up to age 25 years with B-cell precursor ALL that is refractory or in second or later relapse and for adult patients with relapsed or refractory (R/R) large B-cell lymphoma after 2 or more lines of systemic therapy including diffuse large B-cell lymphoma (DLBCL) not otherwise specified (NOS), high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma (Kymriah™ United States Product Insert [USPI], 2018).
- Axicabtagene ciloleucel, approved to treat adult patients with relapsed or refractory large B-cell lymphoma after 2 or more lines of systemic therapy, including DLBCL NOS, PMBCL, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma (Yescarta USPI, 2019).
- Lisocabtagene maraleucel, approved for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after 2 or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified (including DLBCL arising from indolent lymphoma), high-grade B-cell lymphoma, primary mediastinal large B-cell lymphoma, and follicular lymphoma grade 3B (Breyanzi® USPI, 2021).

1.4. JCAR017 Investigational Drug Product

The final JCAR017 investigational drug product includes 2 individually formulated CD8+ CAR + and CD4+ T CAR+ cell suspensions in media containing dimethyl sulfoxide (DMSO) that are thawed and infused separately. JCAR017 is administered by intravenous (IV) infusion.

The CD19-specific CAR and truncated human epidermal growth factor receptor (EGFRt) are introduced into autologous CD8+ and CD4+ T cells ex vivo using a replication-incompetent, self-inactivating lentiviral vector. The CD19-specific CAR includes an scFv binding domain derived from a murine CD19-specific monoclonal antibody (mAb; FMC63) and the 4-1BB and CD3ζ chain signaling domains. The EGFRt protein is expressed as a separate cell surface protein for purposes of cell tracking.

Please refer to the JCAR017 Investigator's Brochure (IB) for detailed information concerning the available pharmacology, toxicology, clinical studies, and adverse event (AE) profile of JCAR017.

1.5. Clinical Experience with JCAR017

Study 017001 is an open-label, multicenter, Phase 1 study to determine the antitumor activity, pharmacokinetics (PK), and safety of JCAR017 in adult subjects with R/R DLBCL NOS (de novo and transformed from indolent lymphoma), high-grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements with DLBCL histology, PMBCL, follicular lymphoma Grade 3B, and MCL. Two disease-specific cohorts are being enrolled: the DLBCL cohort and the MCL cohort. Subjects in the DLBCL cohort must have been treated with an anthracycline and rituximab (or other CD20-targeted agent) and have R/R disease after at least 2 lines of therapy or after autologous-HSCT.

As of 12 April 2019, 255 subjects with DLBCL have undergone lymphodepletion chemotherapy with low-dose fludarabine (30 mg/m^2/day for 3 days) + cyclophosphamide (300 mg/m^2/day for 3 days) (flu/cy), were treated with JCAR017 at Dose Level 1 (50×10^6 JCAR017 cells), Dose Level 2 (100×10^6 JCAR017 cells), or Dose Level 3 (150×10^6 JCAR017 cells) and were evaluable for efficacy. The best response was a CR in 53% of subjects in the efficacy analysis set treated at any dose regimen with efficacy data. Overall, in a total of 268 treated subjects, 42% of subjects experienced cytokine release syndrome (CRS), and 6 subjects (2%) had Grade ≥ 3 CRS (none Grade 5). Neurotoxicity was observed in 30% of subjects, including 10% with Grade ≥ 3 neurotoxicity (none Grade 5) (Abramson 2019).

See the JCAR017 Investigator's Brochure (IB) for further details.

2. STUDY PURPOSE AND RATIONALE

Data from Juno Study 017001 demonstrate that treatment with JCAR017 in subjects with aggressive B-cell NHL who have failed 2 or more lines of therapy results in encouraging efficacy results and an acceptable safety profile. Outcomes of patients who have failed front-line therapy are poor, and additional options are needed. The purpose of this study is to evaluate the use of JCAR017 in subjects who have failed 1 previous line of therapy for aggressive B-cell NHL and are not eligible for HSCT.

2.1. Rationale for JCAR017 Dose Level

As noted in Section 1.5, JCAR017 at flat doses of 50×10^6 CAR+ T cells and 100×10^6 CAR+ T cells has resulted in durable responses and has demonstrated an acceptable safety profile in the third- or greater line treatment of R/R aggressive DLBCL. Additionally, as of 07 Jul 2017, a trend toward improved ORR at 3 months was observed in patients treated at Dose Level 2 (100×10^6 JCAR017 cells) compared to Dose Level 1: 63% (12/19; 95% CI 38, 84) vs 40% (12/30; 95% CI 23, 59). See the JCAR017 IB for more information.

Based on these results, the dose of 100×10^6 CAR+ T cells has been chosen for development in the second-line setting. Depending on available data from ongoing studies at this dose at the time of commencement of subject treatment, the Sponsor may decide to limit enrollment to ensure an adequate safety profile of this dose in the second-line setting.

2.2. Rationale for Study Design

The purpose of this Phase 2 study is to evaluate the efficacy and safety of JCAR017 in adult subjects with aggressive B-NHL who have failed front-line therapy and are not eligible for HSCT. There is no approved standard of care for this population. A non-randomized design was chosen because of the lack of effective therapies in this population (see Section 1.1), leading to concerns about comparing against an ineffective therapy given the promising preliminary efficacy results in third-line subjects (see Section 1.5). Similarly, enrollment to a randomized study versus some assigned treatment is likely to be difficult, given the lack of efficacy of currently-used regimens and the number of clinical studies ongoing in this population.

2.3. Rationale for Lymphodepleting Chemotherapy

As noted in Section 1.5, preliminary data available from subjects with R/R NHL in Study 017001 suggest that the low-intensity lymphodepleting chemotherapy regimen used, cyclophosphamide (300 mg/m^2/day × 3 days) combined with fludarabine (30 mg/m^2/day × 3 days), in combination with JCAR017 has adequate safety and good anti-tumor activity in subjects with R/R NHL. This lymphodepleting chemotherapy regimen was selected to limit toxicity and retain antitumor activity, as well as to optimize cellular expansion and antitumor activity after treatment with JCAR017.

2.4. Rationale for Endpoints

The efficacy endpoints to be assessed in this study are standard endpoints for the assessment of aggressive B-cell NHL. Disease response will be determined according to the

"Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification" (Cheson 2014).

The safety assessments are also standard assessments.

2.5. Risk/Benefit Summary

As discussed in Section 1.1, options for treatment of R/R subjects are limited. Transplant-ineligible subjects have especially limited treatment options as they are not eligible for the most commonly used second-line treatment (HSCT). Administration of JCAR017 has resulted in durable responses in subjects with R/R aggressive DLBCL in Study 017001, suggesting that earlier treatment of subjects with JCAR017 could also provide benefit.

Major safety findings with JCAR017 include severe cytokine release syndrome (sCRS), which has been associated in some studies with higher dose levels of CAR+ T-cell therapy. CRS is characterized by high fever, fatigue, nausea, headache, dyspnea, tachycardia, rigors, hypotension, hypoxia, myalgia/arthralgia, and anorexia, severe (Grade $\geq$ 3) neurotoxicity, and hematological disorders, including neutropenia, thrombocytopenia, and anemia (see the JCAR017 IB for more details). In Study 017001, these toxicities have generally been found to be manageable. A management algorithm for the assessment and treatment of signs of CRS is shown in Appendix F. Guidance regarding management of other safety events is provided in Section 7.

Overall, considering the poor prognosis in subjects for whom HSCT is not an option, and the potential for good responses with JCAR017, the benefit/risk is considered positive in this population.

3. STUDY OBJECTIVES AND ENDPOINTS

The objectives and corresponding endpoints for the study are presented in Table 2. Efficacy analyses will be based on response assessments per the Independent Review Committee (IRC).

Table 2: Study Objectives and Endpoints

Objective	Endpoints
Primary	
• To assess the antitumor activity of JCAR017 in adult subjects with aggressive B-cell NHL who are ineligible for HSCT	• Overall response rate (ORR [CR + partial response])
Secondary	
• To evaluate the safety of JCAR017	• Type, frequency, and severity of AEs and laboratory abnormalities
• To assess the rate of CR and durability of antitumor activity of JCAR017	• CR rate • Duration of response (DOR) and DOR for subjects whose best objective response is CR, each defined as the time from first response to progressive disease (PD) or death
• To estimate the progression-free survival (PFS), event-free survival (EFS), and OS of subjects treated with JCAR017	• PFS, defined as the time from JCAR017 infusion to PD or death • EFS, defined as the time from JCAR017 infusion to the earliest of the following events: death from any cause, PD, or starting a new anticancer therapy • OS, defined as the time from JCAR017 infusion to the date of death
• To characterize the PK profile of JCAR017 in this subject population	• Maximum concentration (C_{max}), time to peak concentration (T_{max}), area under the curve (AUC) and other relevant PK parameters of JCAR017 in blood as assessed by qPCR
• To assess health-related quality of life (HRQoL) and health economics and outcomes research (HEOR)	• Measurement of HRQoL changes as assessed using the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30, the FACT-Lym subscale, and the EuroQol instrument EQ-5D-5L. • Numbers of intensive care unit (ICU) inpatient days and non-ICU inpatient days and reasons for hospitalization
Exploratory	
• To assess immune responses to JCAR017	• Measurement of anti-therapeutic antibodies (ATA) to JCAR017. Cellular immunity may also be assessed.

Table 2: Study Objectives and Endpoints (Continued)

Objective	Endpoints
• To assess the pharmacodynamic effects of JCAR017	• Measurement of pharmacodynamic biomarkers in peripheral blood including, CD19+ B cell enumeration, serum immunoglobulin, soluble biomarkers (cytokines and chemokines), and inflammatory markers (CRP and ferritin)
• To assess CAR T subset expansion and persistence	• Measurement of CD4+ and CD8+ CAR T cell numbers per microliter in blood by flow cytometry
• To assess the effect of JCAR017 attributes on safety, PK, and antitumor activity	• JCAR017 product characteristics (eg, T-cell subsets, transduction efficiency, immunophenotype and gene expression at time of administration and post-dose)
• To assess the effect of tumor and tumor microenvironment on JCAR017 PK and clinical response	• Evaluation of tumor biopsies for CD19 expression and attributes of tumor and tumor microenvironment, including, but not limited to, the presence of T cell subsets and expression of immune checkpoint markers

4. STUDY DESIGN AND INVESTIGATIONAL PLAN

4.1. Overall Study Design

This is an open-label, multicenter, Phase 2 study to determine the antitumor activity, PK, and safety of JCAR017 in subjects who have relapsed from, or are refractory to, front-line immunochemotherapy for aggressive B-cell NHL and are ineligible for transplant. Subjects will be treated with lymphodepleting chemotherapy and JCAR017.

A schematic of treatment for each subject is provided in Figure 1. Upon enrollment, subjects will undergo leukapheresis to enable JCAR017 product generation. A baseline tumor biopsy (either a historical sample, or if not available, a fresh tumor sample) will be obtained. While JCAR017 is being manufactured, if required to control disease, subjects may receive salvage low-dose chemotherapy or one cycle of non-curative standard of care antitumor therapy as described in Section 8.2.2.

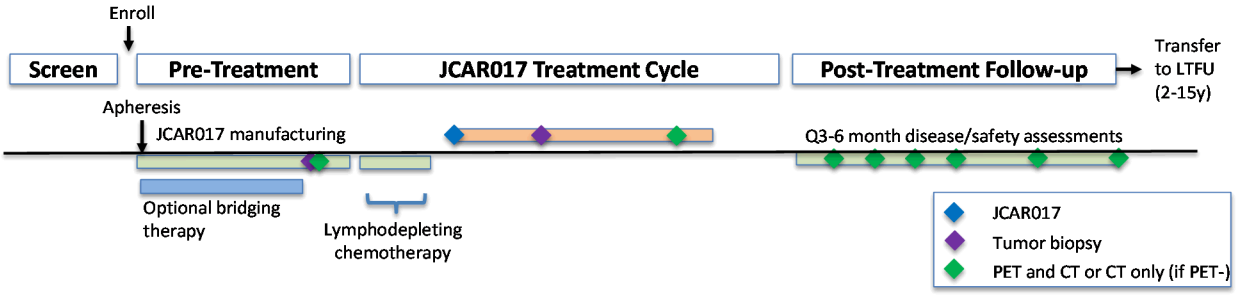
Upon successful JCAR017 product generation, subjects will enter the treatment phase. Treatment includes lymphodepleting chemotherapy with flu/cy followed by JCAR017 administered IV 2 to 7 days after completion of lymphodepleting chemotherapy.

If a subject has achieved a CR to JCAR017 and subsequently progressed, they may receive retreatment only if doses are available and remanufacturing is not required (see Section 8.2.8).

After administration of JCAR017, subjects will enter post-treatment follow-up, and will be followed on this study for 2 years for safety, PK and biomarkers, disease status, HRQoL, and survival, as described in more detail in Section 8. After completion of 2 years of assessments in this protocol, long-term follow-up (LTFU) for survival, long-term toxicity, and viral vector safety will continue under a separate protocol for up to 15 years.

Toxicity will be evaluated on an ongoing basis by the Sponsor and reviewed at regularly scheduled Investigator Safety calls. Additionally, safety monitoring boundaries based on the incidence of Grade 3 or above, JCAR017-related, treatment-emergent neurological toxicity and prolonged Grade 4 and Grade 5 individual safety events will be established using a Bayesian framework (Thall 1994, Yao 2013), as described in Section 10.4 and the Statistical Analysis Plan. If the safety boundaries are crossed, enrollment will be paused and ad hoc Data Safety Monitoring Board (DSMB) meetings will be held to review the data. The study will remain paused for enrollment pending the DSMB recommendations.

Figure 1: Study Schema for Individual Subjects



4.2. Study Duration and Duration of Subject Participation

The duration of study for each subject is approximately 2 years, and the estimated total time from first subject first visit for all subjects to complete the study is approximately 4 years.

4.3. Study Completion

A subject is considered to have completed the study if he/she has completed the last scheduled visit shown in the Schedule of Evaluations.

The end of the study is defined as the date of the last scheduled assessment shown in the Schedule of Evaluations for the last subject in the trial.

4.4. Study Oversight

4.4.1. Data Safety Monitoring Board

An independent DSMB will review cumulative study data approximately semiannually over the course of the study to evaluate safety, protocol conduct, and scientific validity and integrity of the trial. Subject safety will be evaluated, and the DSMB will provide advice to the Sponsor and study Investigators, as specified in the DSMB Charter. Following DSMB meetings, the Sponsor will provide a DSMB review summary to the study Investigators for submission to the site's Institutional Review Board (IRB) within 10 working days of receipt of the statement.

4.4.2. Independent Review Committee

An IRC will be established to determine response and progression status, as described in more detail in Section 8.3.1.

4.5. Suspension or Early Termination of the Study

The study can be suspended or terminated at any time by the Sponsor, the Food and Drug Administration (FDA), at the recommendation of the DSMB, or at the recommendation of an IRB. Circumstances that may warrant suspension or termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to subjects
- Demonstration of efficacy that would warrant stopping
- Determination of futility
- Determination that the primary endpoint has been met
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable

If the study is suspended or terminated for safety reasons, the Sponsor will promptly inform the Investigator, and will also inform the regulatory authorities of the suspension or termination of the study and the reasons for the action. The Investigator may be informed of additional procedures to be followed to ensure adequate protection of subjects. The Investigator will be responsible for promptly informing IRBs, other applicable regulatory committees, and study

subjects of the suspension or early termination of the trial, including the reasons for suspension or termination and any other regulatory committee as applicable.

The study may resume once concerns about safety, protocol compliance, and data quality are addressed to the satisfaction of the Sponsor, IRB, and/or FDA.

5. STUDY POPULATION

5.1. Inclusion Criteria

Subjects must meet all the following criteria to be enrolled into this study:

1. Age ≥ 18 years at the time of consent
2. Signed written informed consent obtained prior to any study procedures
3. Confirmation of R/R aggressive B-cell NHL of the following histologies at relapse:
   a. DLBCL, not otherwise specified (NOS; de novo or transformed follicular lymphoma [tFL]), high-grade B-cell lymphoma (HGL) with MYC and BCL2 and/or BCL6 rearrangements with DLBCL histology (double/triple hit lymphoma [DHL/THL]) or
   b. Follicular lymphoma Grade 3B (FL3B) per WHO 2016 classification (Swerdlow 2016)
4. Previous treatment must include:
   a. Treatment for a qualifying histology (as defined in inclusion criterion 3 above) with a single line of chemoimmunotherapy containing an anthracycline and a CD20-targeted agent, such as R-CHOP
5. Subjects must be deemed-ineligible for both high-dose chemotherapy and HSCT while also having adequate organ function for CAR T cell treatment. To be eligible for this study, subjects must meet **at least ONE** transplant ineligible (TNE) criterion as defined below:
   a. TNE criteria (must meet **at least ONE**):
      (1) Age ≥ 70 years
      (2) Eastern Cooperative Oncology Group (ECOG) performance status = 2
      (3) Impaired pulmonary function: diffusing capacity of the lung for carbon monoxide [DLCO] ≤ 60% adjusted for gender-specific hemoglobin concentration
      (4) Impaired cardiac function: left ventricular ejection fraction (LVEF) < 50%; must be assessed by echocardiogram or multiple uptake gated acquisition (MUGA) scan performed within 4 weeks of determination of eligibility
      (5) Impaired renal function: calculated creatinine clearance (Cockcroft and Gault) < 60 mL/min
      (6) Impaired hepatic function: aspartate aminotransferase (AST)/alanine aminotransferase (ALT) > 2 × upper limit of normal (ULN)
   b. Adequate organ function criteria (must meet **all**):
      (1) SaO2 ≥ 92% on room air AND CTCAE ≤1 dyspnea
      (2) LVEF ≥ 40%
      (3) Calculated creatinine clearance (Cockcroft and Gault) > 30 mL/min

(4) AST/ALT ≤ 5 × ULN

(5) Assessed by the Investigator to have adequate bone marrow function to receive lymphodepleting chemotherapy

(6) Total bilirubin < 2.0 mg/dL (or < 3.0 mg/dL for subjects with Gilbert's syndrome or lymphomatous infiltration of the liver)

6. Positron emission tomography (PET)-positive disease according to the "Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification" (Cheson 2014)
7. Histological confirmation of diagnosis at last relapse. Enough tumor material must be available for central confirmation of diagnosis, otherwise a new tumor biopsy is mandated. NOTE: if subsequent therapies are given after last relapse with SD/PD as best response, the tissue from that last relapse will be considered adequate to participate in the trial.
8. ECOG performance status of 0, or 1, or 2
9. Adequate vascular access for leukapheresis procedure (either peripheral line or surgically-placed line)
10. Females of childbearing potential (FCBP[1]) subjects must:

    a. Either commit to true abstinence[2] from heterosexual contact (which must be reviewed on a monthly basis and source documented) or agree to use, and be able to comply with, effective contraception without interruption. Contraception methods must include 1 highly effective method from screening until at least 12 months after the lymphodepleting chemotherapy.

    b. Agree to abstain from breastfeeding during study participation and for at least 12 months following lymphodepleting chemotherapy.

    c. There are insufficient exposure data to provide any recommendation concerning the duration of contraception and the abstaining from breastfeeding following treatment with JCAR017. Any decision regarding contraception and breastfeeding after JCAR017 infusion should be discussed with the treating physician.

    Note: Highly effective methods are defined as those that result in a low failure rate (ie, less than 1% per year) when used consistently and correctly. The following are examples of highly effective and additional effective methods of contraception:

    - Intrauterine device (IUD)
    - Hormonal (birth control pill, injections, implants)
    - Tubal ligation

[1] A female subject of childbearing potential (FCBP) is a female who: 1) has achieved menarche at some point, 2) has not undergone a hysterectomy or bilateral oophorectomy or 3) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 12 consecutive months (ie, has had menses at any time in the preceding 12 consecutive months).

- Partner's vasectomy

11. Females of childbearing potential (FCBP[2]) subjects must have 2 negative pregnancy tests as verified by the Investigator (one negative serum beta-human chorionic gonadotropin [ß-hCG] pregnancy test result at screening, and within 7 days prior to the first dose of lymphodepleting chemotherapy). This applies even if the subject practices true abstinence[3] from heterosexual contact.
12. Male subjects must:
    a. Practice true abstinence[3] (which must be reviewed on a monthly basis) or agree to use a condom during sexual contact with a pregnant female or a female of childbearing potential for 12 months after lymphodepleting chemotherapy even if he has undergone a successful vasectomy.
    b. There are insufficient exposure data to provide any recommendation concerning the duration of contraception following treatment with JCAR017. Any decision regarding contraception after JCAR017 infusion should be discussed with the treating physician.
13. Subjects must agree to not donate blood, organs, sperm or semen, and egg cells for usage in other individuals for at least 1 year following lymphodepleting chemotherapy. There are insufficient exposure data to provide any recommendation concerning the duration of refraining from tissue donation following treatment with JCAR017. Therefore, subjects treated with JCAR017 should not donate blood, organs, tissues, and cells for transplantation.

5.2. Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from participation in this study:

1. Subjects with central nervous system (CNS)-only involvement by malignancy (note: subjects with secondary CNS involvement are allowed on study)
2. History of another primary malignancy that has not been in remission for at least 2 years. The following are examples of exemptions from the 2-year limit: nonmelanoma skin cancer, definitively treated stage 1 solid tumor with low risk for recurrence, curatively treated localized prostate cancer, and cervical carcinoma in situ on biopsy or a squamous intraepithelial lesion on PAP smear.
3. Previous treatment with CD19-targeted therapy, except prior JCAR017 treatment in this protocol for subjects receiving retreatment
4. Treatment with alemtuzumab within 6 months of leukapheresis, or treatment with fludarabine or cladribine within 3 months of leukapheresis

[2] A female subject of childbearing potential (FCBP) is a female who: 1) has achieved menarche at some point, 2) has not undergone a hysterectomy or bilateral oophorectomy or 3) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 12 consecutive months (ie, has had menses at any time in the preceding 12 consecutive months).
[3] True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. In contrast, periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

5. Active hepatitis B or active hepatitis C infection. (Subjects with a negative polymerase chain reaction [PCR] assay for viral load for hepatitis B or C are permitted; subjects positive for hepatitis B surface antigen [HBsAg] and/or anti-hepatitis B core antibody [HBcAb] with negative viral load are eligible and should be considered for prophylactic antiviral therapy.)
6. History of or active human immunodeficiency virus (HIV) infection at the time of screening
7. Subjects with uncontrolled systemic fungal, bacterial, viral or other infection despite appropriate antibiotics or other treatment at the time of leukapheresis or JCAR017 administration
8. History of any one of the following cardiovascular conditions within the past 6 months: Class III or IV heart failure as defined by the New York Heart Association (NYHA), cardiac angioplasty or stenting, myocardial infarction, unstable angina, or other clinically significant cardiac disease
9. History or presence of clinically relevant CNS pathology such as epilepsy, seizure, aphasia, stroke, severe brain injuries, dementia, Parkinson's disease, cerebellar disease, cerebral edema, organic brain syndrome, or psychosis
10. Pregnant or nursing (lactating) females; subjects must agree to abstain from breastfeeding during study participation and for at least 1 year following lymphodepleting chemotherapy
11. Use of the following:
    - Therapeutic doses of corticosteroids (defined as > 20 mg/day prednisone or equivalent) within 7 days prior to leukapheresis or 72 hours prior to JCAR017 administration. Physiologic replacement, topical, and inhaled steroids are permitted.
    - Cytotoxic chemotherapeutic agents that are not considered lymphotoxic (eg, doxorubicin, vincristine, gemcitabine, oxaliplatin, carboplatin, etoposide) within 1 week of leukapheresis. Oral chemotherapeutic agents, including lenalidomide and ibrutinib, are allowed if at least 3 half-lives have elapsed prior to leukapheresis.
    - Lymphotoxic chemotherapeutic agents (eg, cyclophosphamide, ifosfamide, bendamustine, melphalan) within 2 weeks of leukapheresis
    - Experimental agents within 4 weeks of leukapheresis unless no response or disease progression is documented on the experimental therapy and at least 3 half-lives have elapsed prior to leukapheresis
    - Radiation within 6 weeks of leukapheresis. Subjects must have progressive disease in irradiated lesions or have additional non-irradiated, PET-positive lesions to be eligible. Radiation to a single lesion, if additional non-irradiated PET-positive lesions are present, is allowed up to 2 weeks prior to leukapheresis.
12. Prior hematopoietic stem cell transplant

13. Uncontrolled medical, psychological, familial, sociological, or geographical conditions that do not permit compliance with the protocol, as judged by the Investigator; or unwillingness or inability to follow the procedures required in the protocol
14. Progressive vascular tumor invasion, thrombosis, or embolism
15. Venous thrombosis or embolism not managed on a stable regimen of anticoagulation

5.3. Removal of Subjects from Treatment or Study

At the time of consent, subjects will be advised that they are free to withdraw consent from the study at any time for any reason; however, all subjects who have received treatment with JCAR017 will be encouraged to continue all study evaluations through the End-of-Study (EOS) visit as well as participate in the LTFU study. The Sponsor must be notified if a subject has withdrawn consent from the study or has requested to discontinue treatment, and the reason(s) must be documented.

5.3.1. Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently enrolled in the study. (Enrollment is described in Section 8.2.1). A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, eligibility criteria assessment, and any protocol procedure-related serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened with a new subject number.

5.3.2. Subject Discontinuation Prior to Receiving Study Treatment

Subjects who undergo leukapheresis but do not receive lymphodepleting chemotherapy or JCAR017 will be followed for survival (see Section 8.2.10).

A subject's treatment may not occur for any of the following reasons:

- Subject did not receive study treatment due to disease-related complications
- Subject did not receive study treatment due to interim treatment-related toxicities
- Subject did not receive study treatment because the subject no longer meets eligibility criteria for other reasons (not related to disease or interim treatment)
- JCAR017 could not be manufactured
- Death
- Other

5.3.3. Subject Discontinuation from Further Study Treatment

In the rare event that a subject receives only a partial dose of JCAR017 (eg, CD8 cells only), the subject should be reported as discontinuing treatment. Reasons for discontinuing treatment will include the following:

- AE
- Investigator decision
- Subject decision
- Other

Subjects who are discontinued from treatment will not be withdrawn from the study. The subject will remain on study and continue to have all scheduled evaluations through the EOS visit per the Schedule of Evaluations (see Appendix A).

5.3.4. Subject Withdrawal from Study

A subject may be withdrawn from the study for any of the following reasons:

- Subject withdrawal of consent
- Study termination by Sponsor
- Lost to follow up
- Death
- Other

See the Schedule of Evaluations in Appendix A for data to be collected at the End-of-Study visit.

5.3.5. Replacement of Study Subjects

Subjects who sign the informed consent form but do not receive at least one dose of JCAR017 will be replaced. Subjects who receive nonconforming product (see Section 6.2.3) will be followed per protocol, but will be excluded from certain analysis sets (as noted in Section 10.2) and will be replaced. All enrolled subjects will be assigned a unique subject number.

6. STUDY TREATMENTS

6.1. Lymphodepleting Chemotherapy

The last dose of lymphodepleting chemotherapy must be administered between 2 days and 7 days before JCAR017 administration.

Subjects will be treated with fludarabine (30 mg/m^2/day for 3 days) plus cyclophosphamide (300 mg/m^2/day for 3 days) prior to treatment with JCAR017. Fludarabine dose should be reduced based on renal function (Section 8.2.5.2). See Section 8.2.5.2 for the recommended schedule of administration and for the assessments that will be performed during lymphodepleting chemotherapy. Refer to the most recent package inserts for further details on administration of these agents.

For subjects receiving retreatment, the dose of lymphodepleting chemotherapy may be reduced after discussion with the Sponsor.

6.2. Investigational Treatment: JCAR017

The lisocabtagene maraleucel (JCAR017) investigational drug product is comprised of autologous CD8+ and CD4+ T cells that express a CD19-specific CAR and a truncated epidermal growth factor receptor (EGFRt) that are provided as frozen cell suspensions for IV administration. The JCAR017 investigational drug product is provided as 2 individually formulated CD8+ and CD4+ T cell suspensions in media containing DMSO for direct IV administration in equal cellular quantities into the subject.

The CD19-specific CAR and EGFRt are introduced into autologous CD8+ and CD4+ T cells ex vivo using a replication-incompetent, self-inactivating lentiviral vector. The CD19-specific CAR consists of an scFv binding domain derived from a murine CD19-specific monoclonal antibody (mAb; FMC63) and the 4-1BB and CD3ζ chain signaling domains. The EGFRt protein is expressed as a separate cell surface protein for purposes of cell tracking.

See the JCAR017 Product Manual for details of packaging and labeling, product tracking and accountability, and product disposal and destruction.

6.2.1. Dose and Schedule

The dose of JCAR017 will be 100×10^6 CAR+ T cells. JCAR017 will be administered after lymphodepleting chemotherapy, described in Section 6.1. Subjects must meet the criteria for treatment specified in Section 8.2.5.3. Retreatment with JCAR017 will be allowed in subjects who have achieved a CR and subsequently progress. See Section 8.2.8 for more information.

6.2.2. JCAR017 Preparation, Cell Thawing, and Administration

Each JCAR017 dose consists of CD8+ CAR+ T cells and CD4+ CAR+ T cells, administered separately via IV. The subject must be continuously monitored during each IV administration of JCAR017. Assessments performed on the day of administration are described in Section 8.2.5.4.

Each T-cell suspension (CD8+ cells or CD4+ cells) must be thawed and the labeled dose volume administered into the subject within 2 hours from removal from shipping container or liquid nitrogen (LN2) freezer (if storing product on-site). If JCAR017 has been outside of the shipping

container or LN2 freezer for longer than 2 hours, the product should be withheld and the Sponsor immediately notified.

The dose of CD8+ suspension cells must be administered first and should be immediately followed by the administration of the CD4+ T cells.

See the JCAR017 Product Manual for complete information.

6.2.3. Nonconforming Product

6.2.3.1. Protocol Product Deviation Plan

The JCAR017 Protocol Product Deviation Plan (PPDP) addresses the use of nonconforming investigational product in global clinical trials. The JCAR017 PPDP defines an assessment and decision-making process that permits release to the Investigator and clinical site of drug product that does not meet the specification for certain non-safety related attributes (nonconforming JCAR017). In this process, the Medical Monitor and the Primary Investigator at the clinical site agree that the health of the subject and the risk/benefit profile is acceptable for the subject to receive treatment with the nonconforming investigational product. Development Quality Assurance then assesses the recommendation and is ultimately responsible for the drug product lot disposition. The JCAR017 PPDP is a standalone document.

6.2.3.2. Exception Use of Nonconforming Product

Once a decision is made for the exception use of nonconforming JCAR017, country-specific requirements will be followed for the release of a nonconforming JCAR017 product to treat a subject enrolled in a JCAR017 clinical trial. For example, approval from local health authorities and/or IRBs/ECs will be obtained where required. Any subject will need to provide consent prior to receiving the nonconforming JCAR017 product. While subjects treated with nonconforming product will be followed as per the Table of Events (Appendix A) listed in the protocol, their data will be excluded from the primary safety/efficacy evaluable analysis. Their data will be analyzed separately (Section 10).

Subjects treated with nonconforming product will be replaced for the purposes of study enrollment of per protocol evaluable subjects.

6.3. Avoidance of Bias

This is an open-label, single-armed study. In order to reduce the chance of bias in efficacy evaluations, which could be used to support a registration in this population, an IRC will be used to assess efficacy (see Section 8.3.1).

Investigators involved in the study must declare any relevant financial interests (see Section 11.2.1).

6.3.1. Assignment of Subjects to Treatment Groups

All subjects will be assigned the same treatment.

6.4. Recommended Supportive Care, Additional Treatment, and Monitoring

Acute infusion reactions may occur with administration of JCAR017. Guidelines for the treatment of acute T cell infusion reactions are provided in Section 7.7.

Prophylactic treatment/measures are strongly recommended for subjects at risk for tumor lysis syndrome (TLS), per institutional or clinical standards. Supportive care for the management of CRS is detailed in Appendix F. In some cases, tocilizumab, an anti-IL-6 receptor antibody, may be required to treat toxicities such as severe cytokine release syndrome. Please refer to currently approved RoActemra® prescribing information. As a JCAR017 Investigator, it is important to understand that the JCAR017 Management Guidelines for Cytokine Release Syndrome and Neurotoxicity and the recommended use of tocilizumab is different from the CRS management algorithms for the approved CAR T-cell products. The Sponsor requires that all JCAR017 sites must have at least 2 doses of tocilizumab available prior to infusion for each subject in the initial 30-day post-JCAR017 infusion period. If a site utilizes more than one pharmacy facility, 2 doses of tocilizumab per subject are required in each pharmacy facility. It is recommended to resupply in case tocilizumab is given.

The preferred dose to intervene in subjects with sCRS is 8 mg/kg. Other anti-IL-6 antagonist should be considered in the event of sCRS not responding to tocilizumab. Dosing of any other anti-IL-6 agent should be per the product's prescribing information.

Prophylactic treatment measures for neurological toxicities are detailed in Appendix F.

The use of red blood cells and platelet transfusions, and/or colony-stimulating factors is permitted per institutional or clinical standards.

The use of prophylactic or empiric anti-infective agents (eg, trimethoprim/sulfamethoxazole for pneumocystis pneumonia [PJP] prophylaxis, broad spectrum antibiotics, antifungals, or antiviral agents for febrile neutropenia) is permitted per institutional standards.

Hospitalization may be required after treatment with JCAR017 to manage any treatment-associated toxicities. Subjects who do not have adequate support outside of the hospital or do not have reliable transportation to the clinic for scheduled evaluation or emergencies should be considered for hospitalization for at least the first 7 days following JCAR017 treatment.

6.5. Concomitant Medications

Reporting periods for concomitant medications are summarized in Table 3. Management of potential risks is described in Section 7.

Table 3: Reporting Periods for Concomitant Medications

Reporting Period	What to Record/Report
Initial Informed Consent to first day of administration of lymphodepleting chemotherapy	Medications taken at the time of AEs/SAEs related to protocol-mandated procedures must be recorded/reported
From first day of administration of lymphodepleting chemotherapy to 90 days following last administration of JCAR017, or to EOS visit, whichever is earlier	All medications must be recorded/reported
From 91 days following last administration of JCAR017 until EOS visit	Record/report the following: • Medications used at the time of AEs/SAEs related to JCAR017 and/or protocol-related procedures • Corticosteroids • Medications for the treatment of GVHD • Anticancer therapies

Abbreviations: AE, adverse event; CRF, case report form; EOS, end of study; GVHD, graft versus host disease; SAE, serious adverse event.
Note: Medications and transfusions given, and procedures performed for a pre-existing condition that is ongoing at the time of lymphodepleting chemotherapy should be reported as described in the CRF compliance guidelines (CCGs).

For subjects receiving lymphodepleting chemotherapy but not JCAR017, concomitant medications associated with AEs will be recorded for 30 days following the last dose of lymphodepleting chemotherapy.

The use of prophylactic or empiric anti-infective agents (eg, trimethoprim/sulfamethoxazole for pneumocystis pneumonia [PJP] prophylaxis, broad spectrum antibiotics, antifungals, or antiviral agents for febrile neutropenia) is permitted per institutional standards. Vaccination with an inactivated vaccine is permitted at any time in consultation with the medical monitor.

Subjects should be discouraged from use of illicit drugs, herbal remedies, self-prescribed drugs, tobacco products, or excessive alcohol at any time during the clinical study.

6.5.1. Medications Administered During Hospitalizations

Due to the large amount of data generated during hospitalizations, a targeted concomitant medication collection approach will be utilized for the CRF. Therefore, medications that should NOT be entered on the CRF during inpatient and Intensive Care Unit (ICU) stays are defined in the CRF completion guidelines.

6.6. Prohibited Medications

Chemotherapy given after leukapheresis to maintain disease control must be stopped ≥ 7 days prior to lymphodepleting chemotherapy.

The following medications are prohibited until lack of response, subsequent therapy for lymphoma, or 1 year following JCAR017 treatment, whichever comes first:

- Immunosuppressive medications including, but not limited to systemic corticosteroids at doses exceeding 20 mg/day of prednisone or equivalent, methotrexate, azathioprine, and tumor necrosis factor alpha (TNF-α) blockers.
- Steroids: therapeutic doses (> 20 mg/day of prednisone or equivalent) unless used for treatment of sCRS. Therapeutic doses may be used in life-threatening situations and for other medical conditions when indicated, or after loss of detectable JCAR017 cells. Pretreatment containing steroids may be given for necessary medications (eg, IV Ig) after discussion with the Sponsor. Pre-medication with steroids for JCAR017 administration is not allowed. Physiologic replacement dosing of steroids is allowed. Topical steroids, inhaled steroids, and intrathecal steroids for CNS relapse prophylaxis are permitted.

The following medications are prohibited during the treatment and follow-up periods unless used as an anticancer agent after lack of adequate response to JCAR017 or progression of lymphoma:

- Anticancer agents, excluding lymphodepleting chemotherapy and agents administered as an extraordinary measure to treat AEs of uncontrolled JCAR017 proliferation, sCRS, or neurotoxicity unresponsive to other therapeutic interventions
- Cetuximab, or other anti-EGFR treatments, unless indicated for treatment of uncontrolled JCAR017 proliferation or sCRS
- Experimental agents
- Radiation, unless needed for local control of a single tumor lesion in the presence of other non-irradiated PET-positive lesions

7. POTENTIAL RISKS AND MANAGEMENT OF TOXICITIES

A summary of management of potential treatment toxicity is provided below. See the JCAR017 IB for a complete discussion of potential risks associated with JCAR017. Cytokine release syndrome (CRS) and neurologic toxicities (NT) are associated with CAR T-cell therapies. Celgene has developed specific toxicity management guidelines (TMG) for CRS and NT associated with Celgene cellular products based on current clinical experience across the clinical development programs (Appendix F). These recommendations are based on the CRS revised grading system (Lee, 2014) and the CTCAE and need to be used for grading of CRS and NT to guide management in this trial.

If available and adopted as per site standard practice, CRS and NT grading according to the American Society for Transplantation and Cellular Therapy (ASTCT) Consensus Grading System (Lee, 2019) should also be recorded in the CRF to inform future modifications of the management guidelines.

7.1. Cytokine Release Syndrome

Administration of CAR T cells, such as JCAR017, is associated with CRS. CRS is characterized by high fever, fatigue, nausea, headache, dyspnea, tachycardia, rigors, hypotension, hypoxia, myalgia/arthralgia, and anorexia. Clinical symptoms and severity of CRS are highly variable (Lee 2014), and management can be complicated by concurrent conditions. With JCAR017, CRS usually occurs within two weeks after infusion (Abramson 2017).

- Fever, especially high fever (≥ 38.5°C or ≥ 101.3°F), is a commonly-observed hallmark of CRS, and many features of CRS mimic infection. Hence, infection must be considered in all subjects presenting with CRS symptoms and appropriate cultures must be obtained and empiric antibiotic therapy initiated per institution standard of care.
- Less common symptoms associated with CRS include cardiac dysfunction, adult respiratory distress syndrome, renal and/or hepatic failure, coagulopathies, disseminated intravascular coagulation, and capillary leak syndrome.
- Neurological toxicity has been observed concurrently with CRS.

CRS has been reported in a few cases to be associated with findings of macrophage activation syndrome/hemophagocytic lymphohistiocytosis (MAS/HLH), and the physiology of the syndromes may overlap.

Please refer to Appendix F for a detailed description of CRS, grading, and treatment recommendations. If available and adopted as per site standard practice, CRS and neurological toxicity (NT) grading according to the American Society for Transplantation and Cellular Therapy (ASTCT) Consensus Grading System (Lee, 2019) should also be recorded in the CRF to inform future modifications of the management guidelines.

7.2. Fever

The possibility of CRS should be considered for all subjects with fever ≥ 38ºC or ≥ 100.4ºF following JCAR017 treatment. Subjects should be monitored closely for hemodynamic

instability and changing neurological status. Febrile subjects, neutropenic or otherwise, should be evaluated promptly for infection and managed per institutional or standard clinical practice.

The possibility of CRS should be considered for all subjects with fever following JCAR017 infusion. Subjects should be monitored closely for hemodynamic instability and changing neurologic status.

7.3. Cytopenias

Severe (Grade ≥ 3) cytopenias, including anemia, leukopenia, neutropenia, and thrombocytopenia, can occur with both JCAR017 and lymphodepleting chemotherapy, and delayed recovery has been observed. Complete blood counts (CBCs) should be monitored after JCAR017 infusion until count recovery. Follow institutional guidelines in the event of Grade ≥ 3 cytopenias.

7.4. Infections

Life-threatening and fatal infections have been observed. Severe infections may include bacterial, fungal (including pneumocystis jirovecii), and viral infections (eg, cytomegalovirus, Hepatitis B virus, respiratory viruses, and other viruses). A high index of suspicion is warranted in the event of prolonged or recurrent cytopenias, especially in conjunction with hypogammaglobulinemia, severe lymphopenia, and/or recent use of corticosteroids. Viral reactivation and other serious opportunistic infections should be considered in these settings, and prophylactic, pre-emptive, or symptomatic treatment with antimicrobial, antifungal, anti-pneumocystic, and/or antiviral therapies should be considered per institutional guidelines.

7.5. Neurologic Toxicities

CAR T-cell therapy is associated with unique neurologic toxicities. Neurologic symptoms may include altered mental status, aphasia, altered level of consciousness, and seizures or seizure-like activity. With JCAR017, to date, the start of neurologic symptoms has been noted between 3 to 23 days (median 10 days) (Abramson 2017) after CAR T cell infusion and in severe cases may require admission to the intensive care unit (ICU) for frequent monitoring, respiratory support, or intubation for airway protection. The symptoms are variable generally occur as CRS is resolving or after CRS resolution.

Please refer Appendix F for a detailed description of neurologic toxicities, grading, and treatment recommendations. Note: Tocilizumab is not recommended for the treatment of neurologic toxicities, unless CRS or MAS/HLH is also present.

7.6. Macrophage Activation Syndrome

Macrophage activation syndrome (MAS) is a serious disorder potentially associated with uncontrolled activation and proliferation of CAR T cells and subsequent activation of macrophages (see the JCAR017 IB for further background about MAS).

Macrophage activation syndrome is typically characterized by high-grade, non-remitting fever, cytopenias, and hepatosplenomegaly. Laboratory abnormalities found in MAS include elevated inflammatory cytokine levels, serum ferritin, soluble IL-2 receptor (sCD25), triglycerides, and decreased circulating NK cells. Other findings include variable levels of transaminases, signs of

acute liver failure, coagulopathy, and disseminated intravascular coagulopathy. There are no definitive diagnostic criteria for MAS; it is typically diagnosed using published criteria for hemophagocytic lymphohistiocytosis (Schulert, 2015). While there is considerable overlap in clinical manifestations and laboratory findings between MAS and CRS, other distinguishing MAS physical findings such as hepatosplenomegaly and lymphadenopathy are not common in adult subjects treated with activated T cell therapies.

Subjects treated with JCAR017 should be monitored for MAS, and cytokine-directed therapy should be considered as clinically indicated.

7.7. Infusion Reactions

Administration of JCAR017 may cause infusion reactions, including fever, rigors, rash, urticaria, dyspnea, hypotension, and/or nausea. To minimize the risk of infusion reactions, all subjects should be pre-medicated with acetaminophen and diphenhydramine. Mild infusion reactions should be managed expectantly with antipyretics, antihistamines, and anti-emetics. Corticosteroids should be avoided because of the potential impact on efficacy of infused JCAR017 cells. Rigors may be treated with meperidine.

The following guidelines should be followed for infusion reactions:

- Grade 1: administer symptomatic treatment; continue JCAR017 administration of both CD8+ and CD4+ components at the same dose and rate
- Grade 2: stop administration of JCAR017; administer symptomatic treatment; resume JCAR017 administration of both CD8+ and CD4+ components at a reduced rate only after symptoms resolve
- Grade 3: stop administration of JCAR017, administer symptomatic treatment, and resume JCAR017 administration of both CD8+ and CD4+ components at a reduced rate of administration only after symptoms resolve. If Grade 3 reaction recurs, discontinue JCAR017; no further CD8+ or CD4+ components of JCAR017 should be administered
- Grade 4: discontinue administration of JCAR017 and administer symptomatic treatment as necessary; no further CD8+ or CD4+ components of JCAR017 should be administered

7.8. Tumor Lysis Syndrome

Both the lymphodepleting chemotherapy employed in this protocol and JCAR017 therapy have caused TLS in adult B-NHL subjects with high disease burden. Subjects should be closely monitored for laboratory evidence of TLS (hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia; see Appendix G) and subjects at high risk for developing TLS, such as those with high disease burden and high cell turnover, should receive prophylactic treatment, including administration of allopurinol, rasburicase or equivalent as per institutional guidelines, and hydration, as per standard clinical practice.

7.9. B-cell Aplasia

B-cell aplasia is an expected potential off-tumor, on-target toxicity. Prolonged B-cell aplasia has been observed in other CD19-directed CAR T cell programs (Davila, 2014; Grupp, 2013). Serum immunoglobulin levels will be obtained from all subjects prior to and at various time points following JCAR017 infusion. Hypogammaglobulinemic subjects (serum IgG < 500 mg/dL) should be considered for intravenous immunoglobulin replacement therapy per institutional guidelines.

7.10. GVHD

The likelihood of GVHD occurring with CAR T cell therapy is low, and while it remains a theoretical risk it does not apply to patients enrolled in this protocol (exclusion criterion #12). See the JCAR017 IB for further details.

7.11. Uncontrolled T Cell Proliferation

JCAR017 could theoretically proliferate out of control. If uncontrolled JCAR017 proliferation occurs, subjects may be treated with high-dose steroids (eg, methylprednisolone 1 to 3 g/day, tapered over 1 week) or lymphodepleting doses of cyclophosphamide (1 to 3 g/m^2 IV). If an Investigator suspects uncontrolled JCAR017 proliferation, the Sponsor must be contacted immediately.

7.12. Replication-Competent Lentivirus, Clonality, and Insertional Oncogenesis

Lentiviral vectors used in gene transfer are engineered to be replication-defective; however, generation of replication-competent lentiviruses (RCL) during manufacturing is still a possibility. Modern vector production systems have been improved to reduce the risk of RCL generation. To date, there have been no reports of RCL generated during lentiviral vector manufacturing, which may be due, at least in part, to the use of self-inactivating vectors such as the lentiviral vector used in the production of JCAR017 (Rothe 2013).

Concerns for possible vector integration into the host genome have arisen due to preclinical studies that have shown retrovirus-mediated malignant transformation in mice (Li 2002, Modlich 2005) and monkeys (Donahue 1992), and a single clinical study reporting development of leukemia in subjects with X-linked severe combined immunodeficiency (SCID) who received retroviral-modified CD34+ hematopoietic stem cells (Hacein-Bey-Abina 2003), including one subject who died (Couzin 2005). Of note, no instances of RCL generation during production or lentivirus-mediated malignant transformation in animals or subjects have been reported to date.

Data has recently been published on the integration sites of retroviral and lentiviral vectors used for T cell modification in clinical trials (Wang 2009, Scholler 2012, McGarrity 2013). No clonality of integration sites was observed. In addition, there did not appear to be enrichment of integration sites near genes involved in clonal expansion or persistence.

Per the FDA Recombinant DNA Advisory Committee guidelines (FDA 2000), all subjects will be followed in this study for RCL and vector sequences for up to 15 years following JCAR017 treatment as part of a LTFU protocol. All subjects will be monitored for evidence of unexpected

JCAR017 expansion and the emergence of a new second primary malignancy (SPM), particularly one of T cell origin. Investigators must contact the Sponsor immediately if an unexpected pattern of JCAR017 expansion and/or a new SPM arises.

Second primary malignancies will be monitored as events of interest and must be reported as serious adverse events. This includes any new malignancies, regardless of causal relationship to JCAR017, occurring throughout the subject's entire participation in the study. If a subject develops a new malignancy, the Sponsor will request a tumor sample and blood samples (see the 017006 laboratory manual for details) for causality analysis related to use of integrating vector to determine if insertional oncogenesis is suspected.

7.13. Risks Associated with Lymphodepleting Chemotherapy

Subjects will receive fludarabine and cyclophosphamide prior to treatment with JCAR017 to facilitate lymphodepletion and CAR T cell engraftment. Refer to the package inserts for specific details surrounding the risks of fludarabine and cyclophosphamide.

8. STUDY ASSESSMENTS AND PROCEDURES

A Schedule of Evaluations is provided in Appendix A. Specific visits are described in Section 8.2 and descriptions of study assessments are presented in Section 8.3.

8.1. Schedule of Evaluations

This study will occur in 3 parts: pre-treatment, treatment, and post-treatment.

Pre-treatment includes screening, leukapheresis, and pre-treatment evaluation and begins with assessing subject eligibility for study enrollment. If eligible, the subject will undergo leukapheresis as soon as possible, followed by pre-treatment evaluation prior to lymphodepleting chemotherapy and JCAR017 administration. If needed, subjects may receive treatment between leukapheresis and lymphodepletion as described in Section 8.2.2.

All subjects will receive lymphodepleting chemotherapy prior to JCAR017. All subjects will be assessed for response at approximately Day 29.

Post-treatment includes safety and disease follow-up visits at approximately 2, 3, 6, 9, 12, 18, and 24 months after receiving JCAR017. The Month 24 visit will be the EOS visit.

8.2. Study Visits

8.2.1. Screening (approximately 1-2 weeks prior to leukapheresis)

The screening process begins when the subject signs the IRB-approved informed consent document and continues until the subject is determined to be eligible and the subject is enrolled, or until screen failure is determined. If a subject has had a screening procedure as standard of care within 30 days of consent, it may be used to evaluate study eligibility.

The following assessments will be performed during screening:

- Obtain informed consent (obtained any time before study-related procedures are performed).
- Assess eligibility per inclusion/exclusion criteria. All inclusion/exclusion criteria must be met for subjects to continue in the study.
- Obtain medical history, including: disease diagnosis and history, HSCT history, chemotherapy, radiation and surgical history. If applicable, report/record history of toxicities related to prior treatments and allergies.
- ECOG performance status assessment (see Appendix E)
- Physical examination (see Section 8.3.2)
- 12-lead electrocardiogram (ECG)
- Measure diffusing capacity of the lung for carbon monoxide (DLCO)
- ECHO or MUGA scan
- Local laboratory assessments (see Section 8.3.7):
  - Chemistries

  - CBC w/differential
  - Viral serology
  - Serum ß-hCG pregnancy test on women of child-bearing potential

- PET scan to confirm the presence of PET-positive lymphoma. PET scan may be performed longer than 30 days prior to screening if no intervening anticancer treatments have been performed.
- Collection of tissue from latest archived tumor biopsy (block or slides) for tumor evaluation. If archival sample is before most recent relapse, a new tumor biopsy is mandated to confirm diagnosis.
- IPI (International Prognostic Index)
- Hematopoietic cell transplant specific comorbidity index (HCT-CI)
- HRQoL questionnaires (QLQ-C30, FACT-Lym, and EQ-5D-5L)
- Record all AEs/SAEs related to protocol-mandated procedures and concomitant medications taken at that time (See Section 6.5)

8.2.2. Optional Bridging Therapy for Disease Control Prior to Lymphodepleting Chemotherapy

Subjects may undergo an optional cycle of salvage low-dose chemotherapy (eg, vincristine, rituximab, cyclophosphamide $\leq$ 300 mg/m^2) or non-curative standard of care chemotherapy for disease control prior to leukapheresis and/or while JCAR017 is being manufactured (ie, between leukapheresis and lymphodepleting chemotherapy). Examples of acceptable regimens include:

- Bendamustine plus rituximab (BR)
- Rituximab, cyclophosphamide, etoposide, procarbazine, and prednisone (R-CEPP)
- Rituximab, cyclophosphamide, epirubicin, and prednisone (R-CEOP)
- Rituximab, gemcitabine, cisplatin, and dexamethasone (R-GDP)
- Rituximab and lenalidomide

Other regimens may be acceptable after discussion with the Sponsor.

Any selected regimen should be administered per institutional guidelines. Chemotherapy given after leukapheresis to maintain disease control must be stopped $\geq$ 7 days prior to lymphodepleting chemotherapy, and the washout periods noted in the exclusion criteria (see Section 8.2.3) must be met. The use of therapeutic agents with little/no evidence in the scientific literature for DLBCL should be discussed with the Sponsor. If clinically indicated, local radiation is allowed to a single lesion or subset of lesions if other un-irradiated PET-positive lymphoma lesions are present.

If bridging anticancer treatment is given, subjects must continue to meet eligibility criteria pertaining to adequate organ function, active infections, pregnancy, and washout of prior therapy prior to lymphodepletion. If the subject has not had any cardiotoxic medications or radiotherapy in which fields include the heart, screening assessments of cardiac function (MUGA/ECHO) do

not need to be repeated. The pre-treatment evaluations in Section 8.2.4 noted in parentheses as required must be repeated.

If lymphodepleting chemotherapy is delayed more than 14 days due to recovery from anticancer treatment, the subject must repeat eligibility assessments (some procedures may not be required after discussion with the Sponsor).

8.2.3. Leukapheresis (Approximately 4 Weeks Prior to JCAR017 Administration)

Following enrollment on the study, a leukapheresis collection will be performed on each subject to obtain a sufficient quantity of PBMCs for the production of the JCAR017 investigational product. (See Table 4 for washout periods prior to leukapheresis.) Should a technical issue arise during the procedure or in the immediate processing of the product such that it cannot be used for JCAR017 production, the subject may have subsequent procedure(s) performed (see Section 8.2.3.1).

Table 4: Washout Periods Prior to Leukapheresis

Drug	Washout
Alemtuzumab	6 months
Fludarabine	3 months
Cladribine	3 months
Radiation, multiple lesions	6 weeks
Experimental agents	4 weeks/3 half-lives (whichever is greater)
Lymphotoxic chemotherapeutic agents (eg, cyclophosphamide, ifosfamide, bendamustine)	2 weeks
Radiation, single lesion, if additional non-irradiated PET-positive lesions are present	2 weeks
Rituximab	7 days
Therapeutic doses of corticosteroids (defined as > 20 mg/day prednisone or equivalent)	7 days
Cytotoxic chemotherapeutic agents not considered lymphotoxic (eg, doxorubicin, vincristine, gemcitabine, oxaliplatin, carboplatin, etoposide)	7 days
Oral chemotherapeutic agents (eg, lenalidomide and ibrutinib)	3 half-lives

Leukapheresis should be scheduled as soon as possible after meeting eligibility requirements, in coordination with the Sponsor. Venous access is required for leukapheresis and should be determined according to institutional practice. The following assessments will be conducted:

- CBC with differential on the day of leukapheresis (or within 24 hours prior). CBC must include ALC.
- Vital signs (before and after leukapheresis)
- Cell collection through leukapheresis

- Record all AE/SAEs related to protocol-mandated procedures and concomitant medications taken at that time

8.2.3.1. Assessments Prior to Repeat Leukapheresis

If needed, subjects may undergo additional leukapheresis procedures if JCAR017 was unable to be manufactured. Subjects must continue to meet screening eligibility requirements in order to have a repeat leukapheresis collected. However, it is not necessary to repeat PET scans, MUGA/ECHO, or ECG assessments, or to obtain additional biopsy material, to confirm eligibility. PET/CT scans will need to be repeated following the administration of optional bridging chemotherapy.

8.2.4. Pre-Treatment Evaluation

Unless otherwise noted, pretreatment evaluations must be performed within 7 days prior to lymphodepleting chemotherapy.

The following assessments will be conducted:

- Confirm subject meets study eligibility criteria (see Section 5)
- ECOG performance status assessment (must be repeated after any intervening anticancer therapy)
- Height/weight
- Physical examination with routine neurological exam (must be repeated after any intervening anticancer therapy)
- Vital signs
- 12-lead electrocardiogram (ECG) (must be repeated after any intervening anticancer therapy)
- MMSE (see Appendix D), and Immune Effector Cell-Associated Encephalopathy (ICE) score if performed
- Local laboratory assessments (must be repeated after any intervening anticancer therapy):
  - Serum ß-HCG pregnancy test on all women of child-bearing potential (within 48 hours prior to starting lymphodepleting chemotherapy).
  - Chemistries
  - CBC w/differential
  - Coagulation
  - Inflammatory markers
  - Immunoglobulins
- CT performed at the study site. Must be done within 6 weeks of the start of lymphodepleting chemotherapy, and must be done after any intervening anticancer therapy, as close as possible to the start of lymphodepleting chemotherapy. Not

required if done at the study site for screening within 6 weeks and no intervening anticancer therapy has been administered.

- PET scan performed at the study site. Must be done within 6 weeks of the start of lymphodepleting chemotherapy, and must be done after any intervening anticancer therapy, as close as possible to the start of lymphodepleting chemotherapy. Not required if done at the study site for screening within 6 weeks and no intervening anticancer therapy has been administered.
- Fresh tumor biopsy. If adequate tissue is available from a previous archived tumor biopsy that was performed since the last relapse or since determination of refractory disease, a tumor biopsy will not be required (see the 017006 laboratory manual for details). For subjects with an accessible tumor, a biopsy must be repeated after any intervening anticancer therapy, as close as possible to the start of lymphodepleting chemotherapy.
- Research blood samples (see the 017006 laboratory manual for details):
  - RCL testing
  - Immunogenicity
  - CAR T subset expansion and persistence by flow cytometry
  - PK by qPCR-mediated testing for CAR T cell transgene
  - Biomarkers
- Lumbar puncture or Ommaya reservoir tap for cerebrospinal fluid (CSF) assessment (required for subjects with suspected or confirmed CNS involvement only)
- HRQoL questionnaires (QLQ-C30, FACT-Lym, and EQ-5D-5L) (must be repeated after any intervening anticancer therapy)
- Record all AEs/SAEs related to protocol-mandated procedures and associated concomitant medications (see Section 6.5) (must be repeated after any intervening anticancer therapy)

8.2.5. Lymphodepleting Chemotherapy Through Day 29

8.2.5.1. Criteria for Treatment

Subject eligibility criteria must be confirmed prior to starting the first cycle of lymphodepleting chemotherapy. Low-dose chemotherapy or chemoimmunotherapy given after leukapheresis to maintain disease control must be stopped ≥ 7 days prior to lymphodepleting chemotherapy.

Lymphodepleting chemotherapy will be withheld if calculated creatinine clearance (Cockcroft and Gault; Appendix C) is ≤ 30 mL/min or radioisotope glomerular filtration rate (GFR) is ≤ 30 mL/min. Delay of lymphodepleting chemotherapy by more than 14 days requires discussion with the Sponsor and may require rescreening.

Subjects should not experience a significant worsening in clinical status compared to the initial eligibility criteria that would, in the opinion of the treating physician, increase the risk of adverse

events associated with lymphodepleting chemotherapy or exclude them from treatment with JCAR017 (see Section 8.2.5.3, Criteria for JCAR017 Treatment).

8.2.5.2. Lymphodepleting Chemotherapy (Approximately 5 Days Prior to JCAR017)

Upon notification from the Sponsor that JCAR017 will be available, lymphodepleting chemotherapy should be initiated so as to finish 2 to 7 days prior to JCAR017 administration. Subjects will receive 3 days of fludarabine (30 mg/m^2, unless dose is adjusted as described below) and cyclophosphamide (300 mg/m^2).

The following assessments will be performed on each day before administration of lymphodepleting chemotherapy:

- Vital signs
- Local laboratory assessments:
  - Chemistries
- ECOG performance status (see Appendix E)
- Record all AE/SAEs and concomitant medications (before, during, and after administration)

Antiemetic therapy may be given prior to lymphodepleting chemotherapy per institutional practice. Mesna may be used for subjects with a history of hemorrhagic cystitis per institutional practice.

The recommended order and timing of administration is as follows:

1. The IV hydration is 1 L of 0.9% NaCl given at 500 mL/hr starting 2 hours prior to cyclophosphamide
2. Fludarabine 30 mg/m^2 IV over 30 minutes
   - If creatinine clearance 50 to 70 mL/min: reduce by 20% each daily dose of fludarabine
   - If creatinine clearance 30 to 49 mL/min: reduce by 40% each daily dose of fludarabine
   - Fludarabine should not be administered to subjects with CrCl <30 mL/min.
   - Creatinine clearance (estimated glomerular filtration rate [eGFR] by Cockcroft-Gault, refer to Appendix C) is required within approximately 48 hours of lymphodepleting chemotherapy to assess the need to adjust the dose of fludarabine. Indirect calculation of creatinine clearance should be performed using the Cockcroft Gault formula (Appendix C). Direct measurement of creatinine clearance is also acceptable.
3. Cyclophosphamide 300 mg/m^2 IV over 60 minutes
4. Additional 1 L of 0.9% NaCl given at 500 mL/hr

If subjects had prolonged cytopenias following lymphodepleting chemotherapy during the first treatment, flu/cy conditioning doses may be reduced, after discussion with the Sponsor.

8.2.5.3. Criteria for JCAR017 Treatment

Subjects should not experience a significant worsening in clinical status compared to initial eligibility criteria that would, in the opinion of the treating physician, increase the risk of adverse events associated with JCAR017 infusion. Subjects who meet at least one of the following criteria on the day of scheduled JCAR017 infusion should have JCAR017 administration delayed:

- Suspected or active systemic infection
- Onset of fever ≥ 38°C/100.4°F, not related to underlying disease
- Presence of progressive radiographic abnormalities on chest x-ray, or requirement for supplemental oxygen to keep saturation greater than 91%
- Cardiac arrhythmia not controlled with medical management
- Hypotension requiring vasopressor support
- New-onset or worsening of other non-hematologic organ dysfunction ≥ Grade 3
- Taking any of the prohibited medications as described in Section 6.6
- Progressive vascular tumor invasion, thrombosis, or embolism
- Venous thrombosis or embolism not managed on a stable regimen of anticoagulation

Subjects with active infection must have JCAR017 infusion postponed until the active infection has resolved (subjects with suspected/active infection must have negative culture for at least 24 hours on appropriate antibiotics or negative rapid viral panel). Subjects with organ toxicities may not receive JCAR017 until the organ toxicities have recovered to ≤ Grade 2. In case of delayed infusion, lymphodepleting chemotherapy may need to be repeated after discussion with the Sponsor (see Section 6.1).

In the event that a subject experiences any of the above, the Sponsor must be contacted and discussion regarding delay of treatment must occur.

8.2.5.4. JCAR017 Administration—Day 1 (2 to 7 Days after Completion of Last Dose of Lymphodepleting Chemotherapy)

JCAR017 may be delivered in an outpatient setting at the Investigator's discretion. This setting is not recommended for the following subjects:

- Subjects who do not have adequate caregiver support
- Subjects who are staying greater than 60 minutes from the clinical trial site at the time of treatment.
- Subjects with disease characteristics that, in the Investigators' clinical judgement, puts the subject at higher risk of disease-related complications (eg, TLS)
- Subjects with a psychosocial condition that puts them at risk for not following instructions

If changes to the JCAR017 manufacturing process are made, the Sponsor may mandate that subjects are treated in an inpatient setting until safety is confirmed.

Subjects must meet the criteria for treatment specified in Section 8.2.5.3. Additionally, subjects should be pre-medicated with 650 mg acetaminophen PO and 25 to 50 mg diphenhydramine hydrochloride (PO or IV) 30 to 60 minutes prior to JCAR017 administration. These medications may be repeated every 6 hours as needed based on the Investigator's assessment of symptoms. Pre-medication with steroids is not allowed (see Section 6.6).

Evaluations will be performed as indicated in the Schedule of Evaluations (see Appendix A). Additionally, vital signs will be measured within approximately 5 minutes (±5 min) before and 15 min (±5 min) after infusion, then approximately every 15 min thereafter for the first hour and hourly (±15 min) for the next 2 hours. Continue to monitor vital signs after this point until stable and as clinically indicated (see Section 8.3.4).

Note that subjects who have high baseline tumor burden or high serum lactate dehydrogenase (LDH; ≥ 500 U/L prior to the start of lymphodepletion) have a higher risk for developing neurotoxicity and should be closely monitored (see Appendix F).

8.2.5.5. Day 2 through Day 29

Evaluations will be performed as indicated in the Schedule of Evaluations (see Appendix A).

If subjects develop neurologic symptoms suspicious of and/or diagnosed as neurologic toxicity, subjects will have daily MMSE exams (see Appendix D) and ICE score if performed, until resolution of symptoms.

8.2.6. Follow-up Period: Through Month 24

All subjects, including subjects who withdraw from treatment early and those with progressive disease, will complete the post-treatment follow-up visits at approximately 2, 3, 6, 9, 12, 15* (*only for subjects with a first CR or PR documented at the 3-month evaluation), 18, and 24 months after the JCAR017 treatment for disease status and survival. Evaluations will be performed as indicated in the Schedule of Evaluations (see Appendix A).

8.2.7. Unscheduled Evaluations

If the Investigator feels that a subject needs to be evaluated at a time other than the protocol-specified visit, the subject may be asked to come in to the clinic for an unscheduled evaluation. The following assessments may be performed, as appropriate:

- Physical examination
- Vital signs
- MMSE and ICE score. If subjects develop neurologic symptoms suspicious of and/or diagnosed as neurologic toxicity, subjects will have daily MMSE exams until resolution of symptoms, unless the subject is medically incapacitated and/or medically unable to complete the MMSE (see Section 8.3.3). If ICE scores are taken per institutional practice, those scores should be recorded as well.
- ECOG performance status assessment
- Clinical laboratory evaluations
- PET scan

- CT/MRI scan
- Tumor biopsy (see the 017006 laboratory manual)
- CSF assessment (see the 017006 laboratory manual)
- Research blood samples (see the 017006 laboratory manual):
  - Immunogenicity
  - CAR T subset expansion and persistence by flow cytometry
  - PK by qPCR-mediated testing for CAR T cell transgene
  - Peripheral blood sample for RCL Testing
  - Biomarkers

Additionally, if the Investigator requests any of the following procedures, research samples will be requested:

- CSF assessment
- Pleural, peritoneal, or other relevant fluid sampling
- Tissue sampling
- Autopsy

8.2.8. Retreatment with JCAR017

Retreatment with JCAR017 will be allowed if a subject achieves a CR and subsequently progresses during the post-treatment phase, if the study is open for enrollment, the subject is still eligible, and additional doses of JCAR017 are available and remanufacturing is not required. Upon PD, subjects will have the option to re-consent and must meet eligibility criteria to receive retreatment with JCAR017 (some procedures may not be required after discussion with the Sponsor).

The screening process for retreatment begins on the date the subject signs the IRB-approved retreatment informed consent document. The subject must meet the eligibility criteria of this study.

Subjects will follow the schedule of assessments for screening (some assessments may not be required after discussion with the Sponsor) and upon meeting eligibility criteria, pretreatment evaluations will begin. Post-treatment follow-up will occur per the schedule of assessments after retreatment with JCAR017. Follow-up will continue for 24 months after JCAR017 retreatment.

8.2.9. Assessments on Disease Progression/Relapse

If a subject is found to progress at an unscheduled visit, the following assessments will be performed as soon as possible after disease progression/relapse:

- HRQoL questionnaires (see Section 8.3.10)
- PET scan to confirm disease progression
- Tumor biopsy, as clinically indicated (see the 017006 laboratory manual)

- Bone marrow aspirate and biopsy, as clinically indicated (see the 017006 laboratory manual)
- Research samples (see Section 8.3.9 and the 017006 laboratory manual):
  - Immunogenicity
  - CAR T subset expansion and persistence by flow cytometry
  - PK by qPCR-mediated testing for CAR T cell transgene
  - Biomarkers

8.2.10. Assessments in Subjects Who Undergo Leukapheresis but Do Not Receive Treatment

The date of death for subjects who undergo leukapheresis but do not receive any further treatment on study should be collected in the CRF.

8.2.11. Long-Term Follow-up

Because this protocol involves gene transfer, post-treatment follow-up for lentiviral vector safety, disease status, and long-term survival will continue on this protocol until 24 months after JCAR017 treatment, regardless of disease status, and under a separate LTFU protocol for up to 15 years after JCAR017 treatment.

All subjects who either complete the post-treatment follow-up period specified in this protocol or who prematurely withdraw after at least one dose of JCAR017 will be asked to enroll in the LTFU protocol at the EOS visit or at the time of withdrawal, respectively. A separate informed consent form will be provided for the LTFU protocol. Subjects who discontinue early from this study and do not consent to participate in the LTFU protocol will be followed for survival through public record until their projected end of study visit.

8.2.12. Second Primary Malignancies Follow-up Period

Second primary malignancies will be monitored as events of interest and must be reported as serious adverse events. This includes any second primary malignancies, regardless of causal relationship to JCAR017, occurring throughout the subject's entire participation in the study. If a subject develops a second primary malignancy, the Sponsor will request a tumor sample (refer to laboratory manual) and blood samples (see also Section 7.12 and Section 8.3.9).

8.3. Study Assessments

All study assessments should be performed at the times indicated in the Schedule of Evaluations in Appendix A.

8.3.1. Efficacy Assessments

Treatment response will be assessed by radiographic tumor evaluation at protocol-specified time points by diagnostic quality CT scans (chest, neck, abdomen, and pelvis) and PET scans. PET scans are not required after a subject achieves a CR unless progression is suspected on follow-up CT. Confirmation of PD and assessment of bone marrow involvement by lymphoma will be by

PET scan only; bone marrow aspirates and biopsies will not be required for assessment of disease response. Upon documentation of disease progression or treatment with additional anticancer therapies, radiographic tumor evaluation is no longer required. (Note, PET and CT scans will be read locally and will also be sent to a central imaging laboratory for assessment by an IRC). Disease response will be determined according to the "Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification" (Cheson 2014) as described in Appendix B, as well as other pertinent clinical data as appropriate. Details regarding the IRC are available in the IRC charter.

Treatment decisions will be performed using assessment of response as per the Investigator.

8.3.1.1. Pseudoprogression

If a subject demonstrates early tumor progression (defined as occurring prior to/at 3 months after JCAR017 infusion), the Investigator is responsible for evaluating whether the subject is experiencing a possible pseudoprogression (ie, tumor flare, which is a local inflammatory reaction indicating early tumor response at sites of disease such as lymph nodes) (Cheson 2016).

8.3.2. Physical Examination

Physical examinations must include at a minimum neurological, cardiovascular, pulmonary, and lymph node examinations. In addition, symptom-directed exams should be performed.

The neurological exam should include, at minimum, a physical exam to assess cranial nerves, motor and sensory skills, coordination and balance.

8.3.3. Mini Mental State Examinations/Immune Effector Cell-Associated Encephalopathy Scores

The MMSE (see Appendix D) may be administered by an appropriately trained provider (eg, physician, nurse); a neurologist is not required. Efforts should be made to have the same provider perform the MMSE on a given subject to maintain consistency of assessment. If subjects develop neurologic symptoms suspicious of and/or diagnosed as neurologic toxicity, subjects will have daily MMSE exams until resolution of symptoms, unless the subject is medically incapacitated and/or medically unable to complete the MMSE. If ICE scores are taken per institutional practice, those scores should be recorded as well.

8.3.4. Vital Signs

Vital signs include temperature, respiratory rate, heart rate, blood pressure, and SaO_2 by pulse oximetry.

8.3.5. Tumor Biopsy

Fresh tumor biopsies should be collected at the indicated times in subjects with accessible tumor. Additionally, if a subject develops a new or recurrent neoplasm after treatment with JCAR017, the Sponsor will request a sample of the neoplastic tissue for assessment of RCL.

8.3.6. Adverse Events

Adverse events (AEs) will be collected as described in Section 9.

8.3.7. Clinical Laboratory Evaluations

Screening and other laboratory evaluations (see Table 5) will be performed according to Appendix A. Additional assessments should be performed between scheduled study visits as clinically required in order to diagnose and monitor AEs. See Section 9.4.2 for laboratory abnormality AE reporting rules. The Investigator may choose to repeat any abnormal test in order to rule out laboratory or sample collection error.

Table 5: Analytes for Clinical Laboratory Evaluations

Laboratory Panel	Analytes
Chemistries	Glucose (fasting or non-fasting), blood urea nitrogen (BUN), creatinine, sodium, potassium, β-microglobulin, chloride, calcium, total protein, albumin, total and direct bilirubin, alkaline phosphatase, ALT (SGPT), AST (SGOT), magnesium, phosphate, CO_2, lactate dehydrogenase (LDH), uric acid, triglycerides
Hematology	CBC with differential (manual or automated)
Coagulation	PT/aPTT, INR, fibrinogen, and D-dimer
Viral serology	HIV Hepatitis B (HBsAb, HBsAg, and HBcAb) Hepatitis C (Hep C Ab)
Serum pregnancy	Serum ß-hCG pregnancy test
Inflammatory markers	CRP, ferritin
Immunoglobulins	IgG, IgM, IgA
CSF (if clinically indicated)	Protein, cell counts, glucose

8.3.8. CSF Examination and CNS Symptom Assessment

CSF assessments and CNS imaging (MRI or CT) should be performed before and after JCAR017 administration for subjects with suspected or confirmed CNS involvement, and as clinically indicated (eg, if new CNS symptoms occur, or if clinical signs or suspicion of CNS involvement by lymphoma exists). CSF will be analyzed locally for cell count and differential cytology, and centrally for the presence of JCAR017 (see the 017006 laboratory manual for instructions on sending a sample for JCAR017 testing). CSF cultures (bacterial, fungal, viral) should be performed as clinically indicated for suspicion of infection. Biomarkers may be assessed in CSF as outlined in Section 8.3.9.6.

8.3.9. Research Samples

Testing and analysis of the samples will, generally, follow the Schedule of Evaluations in Appendix A. Allocation of samples to specific testing may be modified where sample material is limited; however, the total volume and type of material collected will not be modified beyond what is described in the laboratory manual.

Detailed information regarding the collection, handling, and shipment of samples for PK, immunogenicity, and biomarker assessment is provided in the 017006 laboratory manual.

8.3.9.1. Immunogenicity Assessments

Immune responses to JCAR017 will be evaluated with an anti-therapeutic antibody (ATA) assay (plasma) to detect the presence of serum antibodies that bind to the extracellular region of JCAR017. In addition, cellular immunogenicity may be evaluated by testing PBMCs from subjects for the presence of anti-JCAR017 cytotoxic T cells.

8.3.9.2. Pharmacokinetic Assessments

Assessment of JCAR017 PK in blood will be determined by qPCR to detect the JCAR017 transgene (see below) and may also be assessed by flow cytometry to enumerate the number and immunophenotype of JCAR017 cells.

8.3.9.3. Viral Vector Sequence Testing

Details regarding sample collection and processing are provided in the 017006 laboratory manual. The presence of vector sequences will be determined by evaluation of blood samples by qPCR. At any time point ≥ 12 months after JCAR017 infusion, if persistence vector sequence is detected in ≥ 1% of cells in two consecutive blood samples, the pattern for vector integration sites will be analyzed. If the integration pattern suggests a predominant integration site, a repeat analysis will be conducted within 3 months and further studies including insertion site analysis will be performed.

If a subject develops a second primary malignancy, the Sponsor will request a sample of the neoplastic tissue for causality analysis related to use of integrating vector to determine if insertional oncogenesis is suspected (see the laboratory manual), and an unscheduled peripheral blood draw for RCL and viral vector sequence testing (see also Section 8.2.12).

8.3.9.4. Biomarker Assessments

Biomarker assessments will be performed to evaluate JCAR017, tumor, and immune system characteristics that may be associated with JCAR017 efficacy and safety. The assessments will include assessment of cytokines and chemokines associated with CRS, neurological toxicity, and immune cell function and tumor and tumor microenvironment characterization. Immunophenotypic, molecular, and/or functional evaluation of JCAR017 and enumeration of immune cell subsets may also be performed.

Cytokines and chemokines will be measured in plasma and may also be measured in CSF as markers of immune activation. Potential correlations between cytokine/chemokine production and efficacy and severity of CRS and neurotoxicity will be assessed.

Immunoregulatory pathways operative in the tumor microenvironment may influence the fate and function of adoptively transferred JCAR017 T cells. Assessment of specific cellular elements within the tumor and the tumor microenvironment will be performed on biopsy samples collected from lymph nodes, and other tumor sites (if accessible), to correlate the presence of these factors with response, duration of response and/or JCAR017 persistence and function. This will include evaluation of JCAR017 infiltration and prevalence, markers of JCAR017 phenotype and function, and location of JCAR017 relative to CD19+ tumor cells.

Flow cytometry and/or mass cytometry may be used to determine the phenotype of JCAR017 cells and to enumerate immune cell subsets in the blood. Analyses to detect tumor cells in

peripheral blood and to analyze tumor cells by flow cytometry may also be performed. These studies aim to identify cellular markers associated with JCAR017 persistence as well as safety and efficacy.

Molecular profiling assessments, including single nucleotide polymorphism (SNP), ATACseq, AbSeq, targeted mutational analysis, whole exome/genome sequencing, and/or gene expression analysis (eg, RNA-Seq) may be conducted on JCAR017 cells, PBMCs and tumor cells in order to identify markers or signatures associated with clinical outcomes. Samples will be obtained pre-treatment, or isolated from peripheral blood, bone marrow aspirates, or lymph node biopsies post-treatment as available.

8.3.9.5. RCL Testing

Replication-competent lentivirus testing will be performed genomic DNA obtained by a peripheral blood draw, and, if positive, confirmed on PBMC if available. Details regarding sample collection and processing are provided in the 017006 laboratory manual. Testing for RCL will utilize a PCR-based assay. Samples for RCL testing will be collected at the time points specified in Appendix A.

If all samples collected within the first year after the final dose of JCAR017 are negative, subsequent samples will be collected and archived. However, if any of the samples are positive, the test will be repeated to confirm the result. If the repeat test is also positive, further analysis of the RCL will be undertaken in order to ascertain the nature of the RCL and potential effects. Subjects with detectable RCL are expected to continue to have blood samples collected and tested until RCL is undetectable. Any confirmed positive result from RCL testing will be reported as an SAE within 24 hours of the Investigator being notified, and as an adverse experience in the form of an Investigational New Drug application (IND) safety report. Relevant health authorities will be notified of the detected RCL in accordance with local guidelines.

Samples will be archived with appropriate safeguards to ensure long-term stability and an efficient system for the prompt linkage and retrieval of the stored samples with the subject's study records and the production lot records. Archived samples will be destroyed as outlined in the separate LTFU protocol.

If a subject develops a second primary malignancy, the Sponsor will request a sample of the neoplastic tissue (see 017001 laboratory manual), and an unscheduled peripheral blood draw for RCL and viral vector sequence testing (see also Section 8.2.12).

8.3.9.6. CSF Examination

CSF samples will be analyzed locally for cell count and differential cytology (see Section 8.3.8), and centrally for the presence of JCAR017 (see the 017006 laboratory manual for instructions on sending a sample for JCAR017 testing).

8.3.10. Health-Related Quality of Life and Health Economics and Outcomes Research

Quality-of-life outcomes will be assessed using the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30, the FACT-Lym subscale, and the EuroQol instrument EQ-5D-5L. Subjects should, whenever possible, complete the questionnaires at the initiation of study visit, prior to any procedure or clinical evaluation. For subjects that do not complete the

questionnaire at any given time point, reason for not collecting will be recorded (eg, too sick/unable to complete, administration error, subject refusal).

If the subject withdraws from the study prematurely, all attempts should be made to obtain final quality-of-life questionnaires prior to subject discontinuation.

8.3.10.1. EORTC QLQ-C30

The EORTC QLQ-C30 is a 30-item scale composed of both multi-item scales and single-item measures. All of the scales and single-item measures range in score from 0 to 100. A higher scale score represents a higher level of well-being and better ability of daily functioning. A 10-point change in the scoring is considered to be a meaningful change in HRQoL. Thus, a high score for a functional scale represents a high/healthy level of functioning; a high score for the global health status/HRQoL represents a high HRQoL, but a high score for a symptom scale/item represents a high level of symptomatic problem.

8.3.10.2. FACT-Lym

The Functional Assessment of Cancer Treatment-Lymphoma (FACT-Lym) consists of the FACT-General scale and a 15-item lymphoma-specific additional concerns subscale (LYM). This scale addresses symptoms and functional limitations that are important to lymphoma patients. Only the LYM subscale will be administered in this study. The LYM items are scored on a 0 ("Not at all") to 4 ("Very much") response scale. Items are aggregated to a single score on a 0-60 scale.

8.3.10.3. EQ-5D-5L

EQ-5D is a standardized measure of health status developed by the EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal. The EQ-5D-5L consists of the EQ-5D-5L descriptive system and the EQ Visual Analogue scale (EQ VAS). The descriptive system comprises dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression). Each dimension has 5 levels (no problems, slight problems, moderate problems, severe problems, extreme problems).

8.3.10.4. Hospital Resource Utilization

Hospital resource utilization will be assessed based on the numbers of ICU inpatient days and non-ICU inpatient days. Dates of and reasons for admission and discharge to the hospital and to the ICU will be collected on the appropriate CRF.

9. SAFETY MONITORING AND REPORTING

The safety of the subjects will be monitored at regular intervals throughout the study by the DSMB as described in Section 4.4 and the DSMB charter.

9.1. Definitions

9.1.1. Adverse Event

In accordance with the International Council for Harmonisation (ICH) E2A guideline, and 21 CFR §312.32, an AE is defined as any untoward medical occurrence in a clinical study subject administered a pharmaceutical product which does not necessarily have a causal relationship with this treatment.

9.1.2. Serious Adverse Event

An SAE is defined as an event that, at any dose, meets any of the criteria in Table 6. Special considerations for SAE reporting are presented in Table 7.

Table 6: Definitions of Serious Adverse Events

Criteria	Description
Fatal:	The AE resulted in death
Life-threatening:	The AE placed the subject at immediate risk of death. (This classification does not apply to an AE that hypothetically might have caused death if it had been more severe.)
Hospitalization/prolongation of hospitalization:	The AE resulted in hospitalization or prolongation of hospitalization. (See Table 7 below.)
Disability/incapacity:	The AE resulted in a disability, significant incapacity, or substantial disruption of the subject's ability to conduct normal life functions
Congenital anomaly/birth defect:	The AE was an adverse outcome in a child or fetus of a subject exposed to the study treatment regimen before conception or during pregnancy
Medically important:	The AE was a medically important event that did not meet any of the above criteria, but may have jeopardized the subject and may have required medical or surgical intervention to prevent one of the outcomes listed above (examples include allergic bronchospasm that required treatment in an emergency room, seizures that do not result in hospitalization, or blood dyscrasias)

Table 7: Special Considerations for SAE Reporting

Hospitalization/prolongation of hospitalization **Note: complications and/or prolonged admissions for routine treatment or procedure do require SAE reporting**	This classification **does not** apply for the following hospitalizations: Admissions for social or situational reasons (eg, no place to stay, live too far away to come for hospital visits) in the absence of any clinical AE Admissions at the discretion of the investigator for administration of lymphodepleting chemotherapy or JCAR017 Admissions for elective or pre-planned treatment for a pre-existing condition that is unrelated to the condition under study and has not worsened since providing informed consent Admissions for routine treatment (eg, platelet transfusion) or monitoring of the condition under study not associated with any deterioration in condition Admissions for routine procedures (eg, bone marrow aspiration) associated with the disease under study **Emergency outpatient treatment or observation that does not result in admission, unless fulfilling other seriousness criteria above**

9.2. Grading and Intensity of Adverse Events

AEs, with the exception of cytokine release syndrome (CRS), will be graded using the NCI CTCAE, Version 4.03 (http://ctep.cancer.gov/reporting/ctc.html). CRS will be graded according to the grading scale adapted from Lee, 2014 (Lee 2014), which is provided in Appendix F.

The reported verbatim term should be the most descriptive medical diagnosis, even if it does not match the CTCAE term used for assigning severity.

AE severity and seriousness will be assessed independently. 'Severity' refers to the intensity of an AE, while 'serious' is a regulatory definition and serves as a guide to the sponsor for defining regulatory reporting obligations.

9.3. Relationship to Study Drug

The assessment of the relationship of an AE/SAE to lymphodepleting chemotherapy and JCAR017 (related or not related) is a clinical decision based on all available information and the following considerations:

Related:	There is a reasonable possibility and/or evidence to suggest a causal relationship between study drug and the AE/SAE and no other more likely alternative cause (concomitant drugs, therapies, disease complications, etc.) is suspected.
Not related:	There is no reasonable possibility and/or evidence to suggest a causal relationship between study drug and the AE/SAE and another more likely alternative cause (concomitant drugs or therapies, disease complications, etc.) is suspected.

9.4. Recording Adverse Events

AEs/SAEs are recorded on the CRF in accordance with the reporting criteria for different time periods as defined in Section 9.5. Each AE/SAE is to be evaluated for:

- Duration (onset and resolution dates)

- Severity, including grade changes during the 90-day period following JCAR017 administration, as per the CRF completion guidelines (see Section 9.2)
- Outcome
- Seriousness (see Section 9.1.2)
- Causal relationship with lymphodepleting chemotherapy or JCAR017 (see Section 9.3)

9.4.1. Recording a Diagnosis Versus Signs and Symptoms

Whenever possible, a unifying diagnosis should be reported as opposed to a listing of individual symptoms. However, symptoms should be grouped into a diagnosis only if each sign or symptom is a medically confirmed component of that diagnosis as evidenced by current standard medical textbooks. If any aspect of a sign or symptom does not fit into a classic pattern of the diagnosis, the individual symptom should be reported as a separate AE/SAE.

One exception to reporting a diagnosis as opposed to symptoms is the event of CRS. If a subject experiences an event of CRS, a diagnosis of CRS and any grade changes for the event of CRS should be reported as an AE. Individual signs and symptoms of CRS and grade changes for those signs and symptoms should be entered as CRS Symptoms in the CRF.

When manifestations of neurological toxicities appear in the presence of CRS or alone, those manifestations should be reported as separate AEs.

9.4.2. Clinical Laboratory Abnormalities and Other Abnormal Assessments

Any laboratory abnormality (eg, clinical chemistry or hematology) or other abnormal assessment findings (eg, ECG or vital signs) that meets any of the following criteria should be recorded as an AE or SAE:

- Requires medical or surgical intervention (including transfusions or growth factors)
- Leads to product discontinuation, delay, or interruption
- Associated with clinical signs and/or symptoms
- Otherwise clinically significant as determined by the Investigator

The clinical diagnosis, rather than the laboratory result or CTCAE term, should be reported by the Investigator (eg, anemia versus low hematocrit, neutropenia versus neutrophil count decreased).

9.4.3. Recording Serious Adverse Events

The following should be considered when recording SAEs:

- Death is an outcome of an event. The event that resulted in death should be recorded in the CRF and reported on the SAE Report Form.
- For hospitalizations for surgical or diagnostic procedures, the illness leading to the surgical or diagnostic procedure should be recorded as the SAE, not the procedure itself.

- When progression of the disease under investigation meets any of the seriousness criteria, it will be reported as an individual SAE. When reporting terms related to disease progression, specific manifestations of the progression (eg, "malignant pleural effusion," "lymphadenopathy from underlying non-Hodgkin's lymphoma") should be reported, rather than the general term "disease progression."

9.4.4. Death Reports

Death is an expected outcome during this study due to the nature of the disease being treated. All deaths must be reported on the Death CRF. Deaths due to progressive disease will not be reported as an SAE unless considered related to a study drug. Any AEs leading to death from the time the subject provides informed consent through 90 days after the JCAR017 infusion should be reported as an SAE according to Table 8.

Deaths that occur more than 90 days after JCAR017 infusion will be captured on the Death CRF and reported as an SAE only if considered related to any study procedure or JCAR017.

9.4.5. Safety Queries

Queries pertaining to SAEs will be communicated from the Sponsor Drug Safety to the site via facsimile or electronic mail. The response time is expected to be no more than ten (10) business days. Urgent queries (eg, missing causality assessment) may be handled by phone.

9.4.6. Pregnancy

All pregnancies or suspected pregnancies (including elevated βhCG or positive pregnancy test in a female subject of childbearing potential regardless of disease state) occurring at any time after receipt of JCAR017 must be reported to the Sponsor within 24 hours of learning of its occurrence. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Celgene Drug Safety immediately by email, phone or facsimile, or other appropriate method, using the Pregnancy Initial Report Form, or approved equivalent form.

Pregnancy follow-up, including all perinatal and neonatal outcomes, should be recorded on a Pregnancy Follow-up Form and should be submitted to the Sponsor within 24 hours of awareness. Any SAE experienced during pregnancy must be reported on the SAE Report Form. Abortion, whether accidental, therapeutic, or spontaneous, should be reported as an SAE. Congenital anomalies or birth defects, as defined by the "seriousness criteria" in Section 9.1.2, should be reported as SAEs.

In the event of a pregnancy occurring in a female subject of childbearing potential or female partner of a male subject, the Sponsor will additionally request information about the mother and child's health during each trimester of pregnancy and for 1 year following the birth of the infant. Please reference the pregnancy information consent (permission) forms for data collection for additional information.

9.5. Reporting Adverse Events to the Sponsor

9.5.1. Reporting Periods for AEs and SAEs

Reporting periods for AEs and SAEs are summarized in Table 8.

Table 8: Reporting Periods for AEs and SAEs

Reporting Period	What to Record/Report
Initial Informed Consent to first day of administration of lymphodepleting chemotherapy	Only AEs/SAEs related to protocol-mandated procedures must be recorded/reported[b]
From first day of administration of lymphodepleting chemotherapy to 90 days following last administration of JCAR017 or to EOS visit, whichever is earlier[a]	All AEs and SAEs must be recorded/reported
For subjects starting a subsequent non-chemotherapy-containing anticancer therapy (eg, checkpoint inhibitors, IMIDs) prior to 90 days following final JCAR017 administration	All AE/SAEs will be collected after initiation of the subsequent therapy for 90 days following final JCAR017 infusion or 30 days following initiation of subsequent therapy, whichever is longer.
For subjects starting a subsequent chemotherapy-containing anticancer therapy prior to 90 days following final JCAR017 administration	Only AEs and SAEs related to JCAR017 and/or protocol-mandated procedures must be recorded/reported after initiation of subsequent therapy
From 91 days following last administration of JCAR017 until EOS visit	All AEs and SAEs related to JCAR017 and/or protocol-mandated procedures must be recorded/reported
From 91 days following last administration of JCAR017 or from start of subsequent anticancer therapy until EOS visit	The following conditions must be reported as SAEs, regardless of relationship to study drug: • Second primary malignancies • New onset or exacerbation of a pre-existing neurologic disorder • New onset of a rheumatologic or other autoimmune disorder • New onset of a hematologic disorder • Rare and unexpected disorders with an unknown etiology (eg, Guillain-Barré, Stevens-Johnson syndrome).

[a] If a subject receives lymphodepleting therapy but not JCAR017, all AE/SAEs should be recorded/reported for 30 days following the last dose of lymphodepleting chemotherapy.
[b] Any clinically significant conditions/events unrelated to study procedures should be reported either in medical history or as an adverse event as described in the CRF completion guidelines.

SAEs will be followed until they resolve or return to baseline; the event stabilizes or is no longer considered clinically significant by the investigator; the subject dies or withdraws consent; or study closure. All non-serious AEs will be followed through the safety reporting period. Certain non-serious AEs of interest may be followed until resolution, return to baseline or study closure.

9.5.1.1. Reporting Timelines for SAEs

All SAEs must be reported within 24 hours of the Investigator's knowledge of the event by facsimile or other appropriate method (eg, via email), using the SAE Report Form, or approved equivalent form. This instruction pertains to initial SAE reports as well as any follow-up reports.

The Investigator is required to ensure that the SAE form is completed in its entirety and that the data on the form is accurate and consistent. This requirement applies to all SAEs (regardless of relationship to investigational product) recorded in the CRF as described in Table 8.

The SAE Report Form should provide a detailed description of the SAE and include a concise summary of hospital records, discharge reports, and other relevant documents. If a subject died and an autopsy was performed, copies of the autopsy report and death certificates are to be sent to Celgene Drug Safety as soon as these become available. If a subject develops a second primary malignancy, copies of the pathology and histology reports are to be sent to Celgene Drug Safety as soon as these become available.

The Investigator is responsible for informing the Institutional Review Board/Ethics Committee (IRB/EC) of the SAE and providing them with all relevant initial and follow-up information about the event. The Investigator must keep copies of all SAE information on file including correspondence with Celgene and the IRB/EC.

Queries pertaining to SAEs will be communicated from Celgene Drug Safety to the site via facsimile or electronic mail. The response time is expected to be no more than 10 business days. Urgent queries (eg, missing causality assessment) may be handled by phone.

10. STATISTICAL METHODS

More details will be provided in the study Statistical Analysis Plan (SAP), which will be finalized prior to any formal data analyses or database lock. A real-world evidence (RWE) SAP will describe how the reference rate p0% for the primary endpoint ORR will be determined from comparable external control data.

10.1. General Considerations

Data from all sites will be combined for the analysis. Post-retreatment data from subjects who received JCAR017 retreatment will be summarized separately. Data from subjects who received nonconforming product will also be summarized separately.

The data generated from Study 017006 (PILOT) will complement the data from BCM-001 Cohort 2 enrolling a similar population in Europe and Japan.

10.2. Analysis Sets

10.2.1. Screened Analysis Set

The Screened Analysis Set will include all subjects who have signed informed consent.

10.2.2. Eligible Analysis Set

The Eligible Analysis Set will include all subjects who have signed informed consent, and who meet all inclusion/exclusion criteria.

10.2.3. Leukapheresed Analysis Set

The Leukapheresed Analysis Set will include all subjects who have signed informed consent and who undergo leukapheresis.

10.2.4. JCAR017-treated Analysis Set

The JCAR017-treated Analysis Set will include all subjects who have received at least one infusion of JCAR017 cell product.

10.2.5. JCAR017-treated Efficacy Analysis Set

The JCAR017-treated Efficacy Analysis Set will include all subjects in the JCAR017-treated Analysis Set who have PET-positive disease present before JCAR017 administration based on IRC assessment. Subjects who do not have baseline PET/CT assessment repeated after bridging therapy and before JCAR017 administration will be excluded from the JCAR017-Treated Efficacy Analysis Set.

10.2.6. Pharmacokinetic Analysis Set

- qPCR Pharmacokinetic Analysis Set

The qPCR PK analysis set includes subjects in the JCAR017-treated Analysis Set who have both baseline and on study PK measurements as assessed by qPCR.

- Flow Cytometry Pharmacokinetic Analysis Set

The flow cytometry PK analysis set includes subjects in the JCAR017-treated Analysis Set who have both baseline and on study PK measurements as assessed by flow cytometry.

10.2.7. Outpatient Analysis Set

The Outpatient Analysis Set includes all subjects in the JCAR017-treated Analysis Set who are monitored as outpatient following JCAR017 administration.

10.2.8. Patient-reported Outcome Analysis Set

- The PRO analysis set will include all subjects who complete their baseline PRO questionnaires and have at least one post-baseline measurement in the JCAR017-treated set.PRO/QoL QLQ-C30 Evaluable Set

The PRO/QoL EORTC QLQ-C30 Evaluable Set includes subjects who have a baseline and at least one post baseline assessment that is analyzable in the JCAR017-treated Analysis Set. The EORTC QLQ-C30 is considered analyzable if at least one subscale is completed.

- The PRO/QoL FACT-LymS Evaluable Set

The PRO/QoL FACT-LymS Evaluable Set includes subjects whose baseline are analyzable and at least one post baseline scale is analyzable in the JCAR017-treated Analysis Set. Questionnaire is analyzable if more than 50% (i.e. a minimum of 8 of the 15 items) are answered.

- The PRO/QoL EQ-5D-5L Evaluable Set

The PRO/QoL EQ-5D-5L Evaluable Set includes subjects who have completed five-dimension measures at baseline and post baseline in the JCAR017-treated Analysis Set.

- The PRO/QoL EQ-VAS Evaluable Set

The PRO/QoL EQ-VAS Evaluable Set includes subjects who have completed visual analogue scale (VAS) at baseline and at post baseline in the JCAR017-treated Analysis Set.

10.3. Planned Analyses

10.3.1. Subject Disposition and Baseline Characteristics

Descriptive summaries of demographics and baseline characteristics will be presented for the JCAR017-treated Analysis Set.

Available demographic and baseline information on such subjects will be listed and summarized.

10.3.2. Primary Endpoint

The primary endpoint of the study is ORR, defined as the proportion of subjects with a best overall response (BOR) of either CR or PR. The best overall response is the best disease response recorded from the time of JCAR017 infusion until disease progression, end of study, the start of another anticancer therapy, or HSCT. Best response will be assigned according to the following order: CR, PR, SD, PD, not evaluable, or not done.

The primary efficacy analysis will test the null hypothesis of ORR $\leq$ p0% against the alternative hypothesis that the ORR > p0% using exact Binomial test with a 1-sided 0.025 level of significance based on the JCAR017-treated Efficacy Analysis Set. The null hypothesis used for

estimating study sample size was derived from a meta-analysis of 2L DLBCL studies with similar but not identical populations compared to the population to be enrolled in the current study. A retrospective patient-level real-world data cohort will be used as a more comparable external/synthetic control to provide the reference rate for the null hypothesis for testing the primary endpoint of ORR. Generation of the external control will be described in the Real-World Evidence (RWE) Study CA082-014 SAP.

Data will be presented for both Investigators' assessments and IRC assessments. Concordance between IRC and Investigator assessments will be summarized by the percent agreement for ORR.

10.3.3. Secondary Endpoints

The secondary endpoints of the study are:

1. The CR rate, defined as the proportion of subjects with a best overall response of CR. The CR rate will be assessed as described for the ORR in Section 10.3.2.
2. DOR from the first response following JCAR017 treatment (see Section 3 for the definition of this endpoint). DOR will be evaluated for subjects who achieve a response. DOR will also be evaluated for subjects whose overall best response is a CR.

   If a subject does not have an event for the DOR analysis, the subject will be censored at the date of the last adequate disease assessments on or prior to the earliest censoring event. The censoring reasons can include ongoing follow-up, discontinuation or completion of the study, receipt of another anticancer treatment.

   Kaplan-Meier (KM) methodology will be used to analyze DOR and DOR for subjects whose best overall response is a CR.
3. PFS, EFS, and OS following JCAR017 treatment (see Section 3 for definitions of these endpoints).

   If a subject does not have an event for the PFS and EFS analysis, the subject will be censored at the date of the last adequate disease assessments on or prior to the earliest censoring event. The censoring reason can include ongoing follow-up, discontinuation or completion of the study, receipt of another anticancer treatment (for PFS only). For assessment of OS, data from surviving subjects will be censored at the last time that the subject is known to be alive.

   Kaplan-Meier (KM) methodology will be used to analyze PFS, EFS, and OS.
4. Maximum concentration (C_{max}), time to peak concentration (T_{max}), area under the curve (AUC) and other relevant PK parameters of JCAR017 (including CD3+, CD4+, and CD8+ CAR-T expressing subsets) in blood

   The PK parameters will be analyzed based on the PK analysis set.

   The PK profile of JCAR017 cells in blood will be characterized, including C_{max}, T_{max}, AUC, and other relevant PK parameters. Expansion of JCAR017 in the blood will be determined (C_{max}), along with the persistence of JCAR017 in the blood, based on the qPCR assay (time above the lower limit of quantification); see Section 8.3.9.

The following PK parameters will be displayed graphically where possible: qPCR-based JCAR017 concentration-versus-time in peripheral blood.

Descriptive statistics for PK parameters will be categorized by clinical response and will include mean, standard deviation, coefficient of variation, minimum, and maximum. Median and ranges of values may be presented for selected variables.

5. HRQoL and HEOR

   The analysis of HRQoL variables will include subjects who have baseline and at least one postbaseline value in the JCAR017-treated Analysis Set.

   In the absence of more specific hypothesis, the global score will be used as the primary HRQoL outcome and physical functional score and fatigue item will be used as secondary outcomes.

   The EORTC QLQ-C30, FACT-Lym, and EQ-5D-5L will be analyzed according to the functional scores and the recommendations in the scoring manual. Scores will be descriptively tabulated (number, mean, standard deviation, median, 95% confidence interval) at each time point with change from baseline and summarized over time by graphical displays. Single items will be also described in terms of number and frequency. Details will be given in the Statistical Analysis Plan (SAP).

   Hospital resource utilization will be assessed based on the numbers of ICU inpatient days and non-ICU inpatient days. Descriptive statistics of ICU inpatient days and non-ICU inpatient days will be provided for subjects in the JCAR017-treated Analysis Set.

10.3.4. Efficacy Subgroup Analysis

Efficacy subgroup analysis will be performed on the following variables:

1. Age: < 65 versus ≥ 65, < 70 versus ≥ 70, and < 75 versus ≥ 75 years at screening
2. Sex: male versus female
3. Ethnicity: Hispanic or Latino versus not Hispanic or Latino
4. Race: white versus other races
5. Prior response status to front-line therapy:
   a. Refractory versus relapsed. The status is refractory if a subject achieved less than a CR to front-line therapy; otherwise the status is relapsed
   b. Refractory disease or relapsed disease ≤ 12 months (defined as CR lasting no more than 12 months) versus relapsed disease later than 12 months (defined as CR lasting more than 12 months).
   c. Refractory (BOR to front-line therapy of PD/SD/PR) or CR lasting < 3 months versus CR lasting ≥ 3 months and ≤ 12 months.
   d. Chemorefractory (BOR to front-line therapy of PD/SD) versus chemosensitive (BOR of CR/PR)
6. CNS disease status: known CNS disease versus no known CNS disease at the time of the first JCAR017 infusion

7. Sum of the products of the perpendicular diameters (SPD) per IRC at pre-lymphodepleting chemotherapy (LDC): < 50 cm^2 versus ≥ 50 cm^2
8. LDH at pre-LDC: < 500 U/L versus ≥ 500 U/L
9. Screening HCT-CI score: ≥ 3 versus < 3
10. Age-adjusted IPI (aaIPI) score: ≥ 2 versus ≤ 1
11. ECOG score at screening: 0 to 1 versus 2
12. Bridging anticancer therapy for disease control:
    a. Yes versus No
    b. Platinum-based regimen versus non-platinum-based regimen versus no bridging regimen
13. NHL subtype: DLBCL NOS, HGL, tFL, FL3B
14. Subgroups defined by age/organ function and disease status as shown in the table below:
    a. Subgroup A versus Subgroup B + C + D
    b. Subgroup A + B versus Subgroup C + D

	Response to 1L therapy of PD/SD/PR or CR lasting ≤ 12 months		
Meets all the following criteria at screening:		**Yes**	**No**
• Age ≤ 75 • ECOG 0-1 • ANC ≥ 1000/ul and platelets ≥ 50,000/ul • ALT ≤ 5 x ULN and total bilirubin < 2.0 mg/dL (or < 3.0 mg/dL if Gilbert's syndrome or lymphomatous infiltration of the liver) • O_2 saturation ≥ 92% and Grade ≤ 1 dyspnea • LVEF ≥ 40% • CrCL > 45 ml/min (or Creatinine < 1.5 x ULN)	**Yes**	A	B
	No	C	D

Abbreviations: 1L = first line; ALT = alanine transaminase; ANC = absolute neutrophil count; CR = complete response; CrCl = creatinine clearance; ECOG = Eastern Cooperative Oncology Group; LVEF = left ventricular ejection fraction; PD = progressive disease; PR = partial response; SD = stable disease; ULN = upper limit of normal

Subgroup analyses will be performed for the primary and secondary efficacy endpoints if there are at least five subjects in each subgroup. Some grouping of classes will be considered if there are too few subjects in some subgroups. Other subgroup analyses will also be performed if deemed appropriate.

10.3.5. Exploratory Endpoints

The exploratory endpoints of the study are listed in Section 3; details of the exploratory analyses are provided in the SAP.

10.3.6. Safety Analysis

Safety analyses will be based on the JCAR017-treated Analysis Set.

10.3.6.1. Adverse Events

All AEs will be listed. The focus of AE summarization will be on treatment-emergent AEs (TEAEs). A TEAE is defined as an AE that starts any time from initiation of JCAR017 administration through and including 90 days after JCAR017 administration. Any AE occurring after the initiation of another anticancer treatment or JCAR017 retreatment will not be considered a TEAE and will be summarized separately. Listings and summaries will be prepared for the following type of events: TEAEs, SAEs, Grade 3 or higher AEs, treatment-related AEs (lymphodepleting chemotherapy, protocol-mandated procedures, or JCAR017), and AEs leading to death. AESIs, including TEAEs of CRS, neurological toxicity, infusion reaction, MAS, TLS, Grade ≥ 3 infection, prolonged cytopenia, as well as post-JCAR017 AEs of hypogammaglobulinemia, autoimmune disorder, and second primary malignancy, will also be summarized. Details of the definition and analysis of the AESIs are provided in the SAP.

Reporting of AEs will be based on the Medical Dictionary for Regulatory Activities (MedDRA) and CTCAE version 4.03 unless otherwise specified in the protocol (eg, grading of CRS [see Appendix F). TEAEs will be summarized by system organ class (SOC), preferred term, and severity. A subject who reports multiple occurrence of TEAEs within the same SOC and preferred term is counted only once using the maximum severity grade for summaries.

COVID-19 AEs, identified by the COVID-19 SMQ with subsequent medical review for internal adjudication, will be summarized by preferred term and toxicity grade. A listing of COVID-19 AEs will be provided.

10.3.6.2. Laboratory Data

All laboratory data will be listed. The focus of laboratory data summarization (including hematology, serum chemistry) will be on treatment emergent laboratory abnormalities. A treatment-emergent laboratory abnormality is defined as an abnormality that, compared to baseline, worsens by at least one grade within 90 days after JCAR017 administration. Local laboratory reference ranges will be utilized for this study. Any abnormality occurring after the initiation of another anticancer treatment will not be considered a treatment-emergent laboratory abnormality. The baseline value is defined as the last available recorded value on or prior to the date of the first dose of investigational product.

If baseline data are missing, then any graded abnormality (ie, an abnormality that is Grade ≥ 1 in severity) will be considered treatment-emergent. Hematological and serum biochemistry data will be graded according to CTCAE Version 4.03, when applicable. Grade 0 includes all non-missing values that do not meet the criteria for an abnormality of at least Grade 1. Grade 5 will not be used. Some laboratory tests have criteria for both increased and decreased levels; analyses for each direction (ie, increased, decreased) will be presented separately.

10.3.6.3. Safety Subgroup Analysis

In the JCAR017-treated Analysis Set, safety subgroup analyses will be performed on the same variables as specified in Section 10.3.4. Subgroup analyses will be performed for key safety summaries and will only be performed if there are at least five subjects in each subgroup. Some grouping of classes will be considered if there are too few subjects in some subgroups. Other subgroup analyses will also be performed if deemed appropriate.

10.4. Safety Monitoring Boundaries

Safety monitoring boundaries based on Bayesian framework (Thall 1994, Yao 2013) have been included to help detect safety signals that may occur in the study. These boundaries are non-binding and the following toxicity events occurring within 30 days of a JCAR017 cell product infusion will be considered as safety events of interest for monitoring:

- A Grade 3 or above, JCAR017-related, treatment-emergent neurological toxicity
- Prolonged Grade 4 and Grade 5 individual safety events

Whenever the safety boundaries are crossed, enrollment will be paused and ad hoc DSMB and SC meetings will be held to review the data. The study will remain paused for enrollment pending the DSMB and SC's recommendations.

More information is available in the Statistical Analysis Plan.

10.5. Sample Size Considerations

A sample size of approximately 62 subjects in the JCAR017-treated Efficacy Analysis Set provides at least 85% power to reject the null hypothesis of overall response rate less than 50% assuming the target response rate of 70% using an exact binomial test with 1-sided significance level 0.025. EAST v6.4.1 is used to calculate the sample size and power.

The assumption of the null hypothesis of 50% ORR is supported by the literature and meta-analysis presented in Section 1.1. This meta-analysis shows an ORR of 46% (95% CI: 0.43, 0.50) using the fixed-effect model and 52% (95% CI: 0.44, 0.59) using the random-effects model. Of note, the patient population in these studies included a mixture of diagnoses, numbers and types of prior lines of therapy, and patient performance status, and did not exactly match the population to be enrolled in the current study. A retrospective patient-level real-world data cohort is being planned to generate a comparable external/synthetic control from a real-world evidence (RWE) study, which will be used to provide a null hypothesis for testing the primary endpoint of ORR. Generation of this external control will be discussed in detail in a separate RWE Statistical Analysis Plan. Table 9 shows the power to reject the null hypothesis of a response rate $\leq$ p0% (a potential range of estimates from the retrospective patient-level real-world cohort) assuming the target response rate (pa) of 70% using an exact binomial test with 1-sided significance level 0.025 with a sample size of 62 subjects from both studies.

Table 9: Power Calculation for Rejecting the Null Hypothesis Over a Range of Potential Overall Response Rate Estimates from the Retrospective Patient-Level Real-World Cohort, Assuming a Target Response Rate of 70% Using an Exact Binomial Test with 1-Sided Significance Level 0.025 and a Sample Size of 62 Subjects

pa	p0%	Power
70%	45%	96.9%
70%	47.5%	94.6%
70%	50%	86%
70%	52.5%	79.1%
70%	55%	60.5%

Abbreviations: pa, overall response rate in JCAR017-treated Efficacy Analysis Set; p0, overall response rate from retrospective patient-level real-world cohort.

EAST v6.4.1 is used to calculate the power.

10.6. Timing of Analyses

Administrative efficacy analyses may be performed per health authorities' request without any intention for hypothesis testing or change of study conduct. Therefore, no adjustments for multiplicity are needed. Interim data may be analyzed and presented at scientific meetings.

10.6.1. Primary Analysis

The primary analysis is planned after approximately 62 subjects have been treated with JCAR017, and these subjects have been followed for at least 6 months after first response (either CR or PR), or until death, progressive disease, or withdrawal from study. Hypothesis testing will only be performed at the time of the primary analysis.

10.6.2. Final Analysis

The final analyses will be carried out after all subjects in Study 017006 have completed or discontinued the study due to any reason. No formal hypothesis testing will be performed at the final analysis.

10.7. Data Collection System

An EDC system provided by the Sponsor will be used for data collection. The EDC system is a fully validated, secure system that conforms to 21 CFR Part 11 requirements. Access to the EDC system is role-based, and login credentials will be provided only after completion of the assigned role-based training.

10.8. Data Quality

Study site personnel will enter data into the CRFs in the EDC system. A Sponsor Clinical Research Associate (CRA) or designee will verify data recorded in the CRFs with the source documents.

To ensure complete and accurate data, automated data validation checks programmed within the EDC system will flag missing and nonconformant data during data entry. Data review by the Sponsor project team may result in additional questions. Items flagged by the automated data validation checks and by the project team will appear as electronic queries on the applicable CRF in the EDC system for a specified user role to resolve. All data entry and subsequent data changes are logged in an audit trail in the EDC system.

The Principal Investigator is responsible for ensuring that the data entered into the CRFs are complete and accurate and will electronically sign the CRFs for each subject prior to database lock.

Following database lock, an electronic copy of the final subject casebook will be provided to the study site for archival.

11. STUDY ADMINISTRATION

11.1. Regulatory and Ethical Considerations

11.1.1. Regulatory Authority Review

The study will be conducted in accordance with Good Clinical Practice (GCP), the protocol, and any other applicable Federal, state, and/or local regulatory requirements.

11.1.2. Institutional Review Board/Independent Ethics Committee Approval

It is the responsibility of the Investigator to ensure that the appropriate IRB has reviewed and approved this protocol prior to initiating the study. The IRB must also review and approve the investigative site's informed consent form (ICF), other written information provided to the subject, and all subject materials that may be used.

If the protocol, Investigator's Brochure, or ICF are amended during the study, per local regulations the Investigator is responsible for ensuring that the IRB has reviewed and approved these amended documents. In addition, IRB approval of the amended documents must be obtained before implementation and before new subjects are consented to participate in the study using the amended version of the ICF.

11.1.3. Institutional Biosafety Committee Approvals

JCAR017 consists of autologous T cells that have been manipulated via genetic modification in vitro to express a CAR directed against the CD19 cell surface marker. Since neither the subject source material nor the final investigational drug product has been tested for the presence of communicable diseases in accordance with the provisions in 21 CFR §1271.90(a)(1), the JCAR017 investigational drug product should be handled according to institutional procedures for materials that may contain infectious materials (eg, BioSafety Level 1 or 2).

It is the responsibility of the Investigator to ensure that the appropriate Institutional Biosafety Committee (IBC) has reviewed and approved this protocol, protocol amendments, and any other required materials prior to initiating the study if required per institutional policy.

Each site will be approved by the IBC in accordance with local procedures and country-specific regulatory requirements. Documentation of IBC approval must be in place prior to JCAR017 shipment to the site.

11.1.4. Subject Informed Consent

The Investigator, or a qualified person designated by the Investigator, must obtain informed consent of a subject and/or a subject's legal representative prior to any study-related procedures.

Documentation that informed consent occurred prior to the study subject's entry into the study and of the informed consent process should be recorded in the study subject's source documents including the date. The original ICF signed and dated by the study subject and by the person consenting the study subject prior to the study subject's entry into the study, must be maintained in the Investigator's study files and a copy given to the study subject. In addition, if a protocol is amended and it impacts on the content of the informed consent, the ICF must be revised. Study subjects participating in the study when the amended protocol is implemented must be

re-consented with the revised version of the ICF. The revised ICF signed and dated by the study subject and by the person consenting the study subject must be maintained in the Investigator's study files and a copy given to the study subject.

11.2. Investigator Obligations

11.2.1. Investigator Responsibilities

The Investigator is responsible for ensuring that all study site personnel, including Sub-Investigators and other responsible study staff members, conduct the study in compliance with the Declaration of Helsinki and the ICH E6 Guideline for GCP, including the archiving of essential documents.

The Investigator will ensure adherence to the basic principles of Good Clinical Practice, as outlined in 21 CFR 312, Subpart D, "Responsibilities of Sponsors and Investigators," 21 CFR, Part 50, 1998, and 21 CFR, Part 56, 1998.

The Investigator, Sub-Investigators, and key study staff as listed on FDA form 1572 will comply with 21 CFR, Part 54, 1998, providing documentation of any financial conflict of interest. This documentation must be provided prior to the Investigator's (and any Sub-Investigators) participation in the study. The Investigator and Sub-Investigator(s) agree to notify the Sponsor of any change in reportable interests during the study and for 1 year following completion of the study at the Investigator's site. Study completion at a site is defined as the date when the study database is locked.

If necessary to amend either the protocol or the study ICF, the Investigator will be responsible for ensuring that the IRB reviews and approves the amended documents, and that subjects are informed of applicable changes, and updates.

The Investigator will sign and return to the Sponsor the "Protocol Signature Page" of the original protocol and any protocol amendment, provide current medical licenses, curriculum vitae, and the US FDA form 1572 "Statement of Investigator." All forms must be updated as applicable throughout the study.

11.2.2. Investigator Reporting Requirements

In accordance with applicable regulatory requirements, the Investigator is solely obligated to inform the IRB of progress of the study and notify the IRB of study closure. The Investigator must also provide the Sponsor with copies of all IRB correspondence that relate to study approvals, updates, or changes. The Investigator must also forward all IRB renewals to the Sponsor.

11.3. Access to Information for Monitoring

Site monitoring is necessary to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with ICH GCP, and with applicable regulatory requirement(s). In accordance with regulations and guidelines, the designated Sponsor CRA must have direct access to the Investigator's source documentation

(including medical records, test and procedure results, Investigator and study staff notes, etc.) in order to verify the accuracy of the data recorded in the CRF.

The CRA is responsible for routine review of the CRFs at regular intervals throughout the study to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them. The CRA should have access to any subject records needed to verify the entries on the CRFs. The Investigator agrees to cooperate with the CRA to ensure that any problems detected through any type of monitoring (central, on site) are resolved.

11.4. Site Audits and Regulatory Inspections

Representatives of regulatory authorities, the Sponsor, or IRB may conduct inspections or audits of the clinical study. If the Investigator is notified of an inspection by a regulatory authority, the Investigator agrees to notify the Sponsor Study Manager immediately. The Investigator agrees to provide to representatives of a regulatory agency or the Sponsor access to records, facilities, and personnel for the effective conduct of any inspection or audit.

11.5. Protocol Deviations

Protocol deviations must be sent to the site's IRB per their policies. The Investigator is responsible for knowing and adhering to the institution's IRB requirements.

COVID-19-related protocol deviations will also be summarized and listed in a similar fashion as described above.

11.6. Quality Assurance and Quality Control

The Sponsor or its designee will perform quality control and quality assurance checks of all clinical studies that it sponsors. Before the enrollment of any subject in this study, the Sponsor personnel will review and provide training as needed to the Investigator, Sub-Investigators, and study site personnel regarding the following: protocol, IB, CRFs and procedures for their completion, informed consent process, and procedures for reporting SAEs. Site visits will be performed by the Sponsor CRAs or designees periodically throughout the study. During these visits, information recorded on the CRFs will be verified against source documents, and requests for clarification or correction may be made. The CRFs will be reviewed by the CRA for safety information, completeness, accuracy, and logical consistency. Computer programs that identify data inconsistencies may be used to help monitor the clinical study. Requests for clarification or correction will be sent to Investigators via data queries.

11.7. Public Notification of Study Conduct

Consistent with Section 113 of the Food and Drug Modernization Act of 1997 (FDAMA) and with requirements of the International Committee of Medical Journal Editors (ICMJE) as a condition of consideration for publication of study results, the Sponsor will be responsible for ensuring that this protocol is listed at the ClinicalTrials.gov website per the US FDA requirement and that information at the website relating to study design and conduct is appropriately updated during the course of the study.

11.8. Study Completion

Upon completion or early termination of the study, the following activities, when applicable, must be conducted by the CRA and the Investigator:

- Return of all electronic and any non-electronic study data to the Sponsor, if requested;
- Data clarifications and/or resolutions;
- Accounting, reconciliation, and final disposition of used and unused study drug; and
- Review of site study records for completeness.

In addition, the Sponsor reserves the right to temporarily suspend or prematurely terminate this study for any reason (see Section 4.5).

11.9. Site Termination

The Sponsor has the right to terminate a study site at any time for various reasons. Study termination and follow-up will be performed in compliance with the conditions set forth in 21 CFR Parts 312.50 and 312.56 and local regulation.

11.10. Records Retention

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. Records of subjects, source documents, monitoring visit logs, inventory logs of study investigational product, regulatory documents, and other Sponsor correspondence pertaining to the study must be kept in the appropriate study files at the site. Source documents include all recordings and observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical study. This includes any electronic records. These records will be retained in a secure file for the period required by the institution or site policy but not less than 25 years. Prior to the transfer or destruction of these records, the Sponsor must be notified in writing and be given the opportunity to further store such records.

11.11. Confidentiality of Information

Individual subjects and their research data will be identified by a unique study identification number. Subjects' names will remain confidential and will not be included in the database. This confidentiality extends to testing of biological samples and genetic tests in addition to the clinical information relating to subjects. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the Sponsor. The Investigator will maintain a personal subject identification list (subject numbers with the corresponding subject names) to enable records to be identified.

For tracking purposes and product chain of custody, subjects' name and name and date of birth will be communicated to the study sponsor's scheduling and manufacturing staff. This information will also be listed on the leukapheresis cell collection bag, and other containers throughout the JCAR017 manufacturing process. This information will be maintained in a

separate limited-access database and not together with any other clinical information. Only staff who need to use this information will have access to it.

11.12. Future Use of Stored Specimens and Data

Samples of blood and/or tissue collected during this study may be stored for future research at the Sponsor in subjects who provide consent. The purpose of this future research would be to evaluate tumor and immune system characteristics that may be associated with the efficacy and safety of future therapeutic advancements in this or other disease settings and/or for product development related to JCAR017 or closely related products. The expected testing may include immunophenotypic evaluation of immune cell function, tumor and tumor microenvironment characterization, enumeration of immune cell subsets, and assessment of cytokine, chemokine, and other plasma-soluble factors.

Molecular profiling techniques, including, but not limited to, single nucleotide polymorphism (SNP), ATACseq, AbSeq, targeted mutational analysis, whole exome/genome sequencing, and/or gene expression analysis (eg, RNA-Seq) may be conducted on these samples in order to identify genetic markers or gene expression signatures that could influence the impact of future therapeutic advancements.

In addition, future analyses may include the assessment of specific cellular elements within the tumor, tumor microenvironment, and adjacent tissue space with the specific goal to understand how these factors might influence the response and function of future therapeutic advancements in this or other disease areas for JCAR017 or closely related products.

11.13. Publication Plan

Interim data from this study may be presented at scientific meetings. The Sponsor is responsible for the Study 017006 final clinical study report (CSR) prepared according to ICH guidelines. A final CSR will be prepared and will include any subject who has signed informed consent, regardless of whether the study is completed or prematurely terminated. If appropriate, an abbreviated or synoptic report may be prepared. The CSR will be in compliance with any applicable regulatory requirements and national laws and will be written in English.

11.14. Conflict of Interest

Any potential conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed in accordance with 21 CFR Part 54 (see Section 11.2.1).

12. CONTACT INFORMATION

12.1. Study Sponsor

Juno Therapeutics, Inc.
A wholly owned subsidiary of Celgene Corporation
400 Dexter Ave North, Suite 1200
Seattle, WA 98109
Phone: 206-582-1600
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12.2. Global Drug Safety

Pharmacovigilance at Celgene Corporation:
Email: [redacted] or fax: [redacted]

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APPENDIX A. SCHEDULES OF EVALUATIONS

STUDY 017006: SCREENING ASSESSMENTS	
Obtain consent	x
I/E criteria (5)	x
Medical history	x
ECOG	x
Physical exam (8.3.2)	x
12-lead ECG	x
DLCO	x
MUGA/ECHO	x
Viral serology (8.3.7)	x
Serum pregnancy[d] (8.3.7)	x
PET scan[a] (8.3.1)	x[a]
CBC w/differential (8.3.7)	x
Chemistries (8.3.7)	x
Tumor biopsy[b]	x
IPI	x
HCT-CI[c]	x
HRQoL questionnaires[c] (8.3.10)	x
Record all AEs/SAEs related to study procedures and concomitant medications taken at that time	x

Abbreviations: AE, adverse event; CBC, complete blood count; DLCO, diffusing capacity of the lung for carbon monoxide; ECG, electrocardiogram; ECHO, echocardiogram; ECOG, Eastern Cooperative Oncology Group; HCT-CI, hematopoietic stem cell transplant-specific comorbidity index; HRQoL, health-related quality of life; I/E, inclusion/exclusion; IPI, International Prognostic Index; MUGA, multigated acquisition scan; PET, positron emission tomography; SAE, serious adverse event.

[a] PET scan may be performed more than 30 days prior to screening if no intervening anticancer treatments have been performed.

[b] Collection of tissue from latest archived tumor biopsy (block or slides) for tumor evaluation. If archival sample is before most recent relapse, a new tumor biopsy is mandated to confirm diagnosis.

[c] Not required to determine eligibility, but required prior to commencing any further therapy.

[d] Pregnancy test for females of childbearing potential.

Note: If a subject has had a screening procedure as standard of care within 30 days of consent, it may be used to evaluate study eligibility after discussion with the Sponsor.

STUDY 017006: LEUKAPHERESIS ASSESSMENTS	
CBC w/differential (8.3.7) on the day of (or within 24 hours prior to) leukapheresis. CBC must include ALC	x
Vital Signs (8.3.4), before and after leukapheresis	x
Leukapheresis (8.2.2)	x
Record all AEs/SAEs related to study procedures and concomitant medications taken at that time	x

Abbreviations: AE, adverse event; ALC, absolute lymphocyte count; CBC, complete blood count; SAE, serious adverse event.

STUDY 017006: PRETREATMENT, TREATMENT, AND POSTTREATMENT ASSESSMENTS																		
	Pretreatment Period	**Treatment Period**									**Post-Treatment (Follow-Up, Disease Progression, EOS) Note: efficacy evaluations (CT, PET) not required after PD or subsequent anticancer treatment**							
Study Day	**Within 7 days prior to lymphodepletion**	**Lymphodepletion: Ending day -7 to -2[f]**	**1[f]**	**4**	**8**	**11**	**15**	**22**	**29**	**60**	**90**	**180**	**270**	**365**	**455[v]**	**545**	**PD**	**730 (EOS)**
Month	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**	**2**	**3**	**6**	**9**	**12**	**15**	**18**	**N/A**	**24**
Visit Window (days)				± 1	± 1	± 1	± 2	± 2	± 2	± 14	± 14	+ 35	+ 35	+ 35	± 14	± 14	N/A	± 14
Procedure (protocol section)																		
I/E criteria (5)	x																	
ECOG	x	x	x		x		x	x	x									
Height/Weight	x		x[h]															
Physical exam (8.3.2)	x		x[j]	x[j]	x[j]	x[j]	x[j]	x[j]	x[j]	x[j]	x[m,n]	x[m,n]	x[m,n]	x	x[m,n]	x[m,n]		x
Vital signs (8.3.4)	x	x[g]	x[i]	x	x	x	x	x	x									
12-lead ECG (if chemo since screen)	x																	
MMSE (8.3.3) [x]	x		x	x	x	x	x	x	x	x	x[m]							
HRQoL questionnaires (8.3.10)	x		x						x	x	x	x	x	x	x	x	x	x
Serum pregnancy (8.3.7)	x[a]										x[w]	x[w]	x[w]	x[w]				
Lymphodepleting chemo (8.2.5.2)		x[g]																
JCAR017 administration (8.2.5.4)			x[t]															
Tumor biopsy (8.3.5)	x[b]					x[k]											x	
CT (8.3.1)	x[c]								x[l]		x[m]	x[m]	x[m]	x[m]	x[m]	x[m]		x[m]
PET (8.3.1)	x[c]								x[l]		x[m,n]	x[m,n]	x[m,n]	x[m,n]	x[m,n]	x[m,n]	x	x[m,n]
MRI of brain	x[e]								x[d]		x[d]	x[d]	x[d]	x[d]	x[d]	x[d]		x[d]
CBC w/differential (8.3.7)	x		x	x	x	x	x	x	x	x[u]	x[u]	x[u]	x[u]	x[u]	x[u]	x[u]		x[u]
Coagulation (8.3.7)	x		x	x	x	x	x	x	x									
Chemistries (8.3.7)	x	x[y]	x	x	x	x	x	x	x									
Inflamm. Markers (8.3.7)	x		x	x	x	x	x	x[d]	x[d]									
Immunoglobulins (8.3.7)	x						x	x	x	x[s]	x[s]	x[s]	x[s]	x[s]	x[s]	x[s]		x[s]
Peripheral blood sample for immunogenicity (8.3.9)	x						x		x	x[m]	x[m]	x[m]	x[m]	x[m]	x[m]	x[m]	x	x[m]
Peripheral blood sample for persistence and expansion by flow (8.3.9)	x		x	x	x	x	x	x	x	x	x	x	x	x	x		x	
Peripheral blood sample for qPCR-based PK (8.3.9)	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x[o]	x[o]	x[o]
Peripheral blood sample for biomarkers (8.3.9)	x		x	x	x	x	x	x	x	x[m]	x[m]	x[m]	x[m]	x[m]	x[m]	x[m]	x	x[m]
Peripheral blood sample for RCL testing (8.3.9)	x										x	x		x	x			x
CSF assessment (8.3.9.6)	x[e]								x[e]		x[e]	x[e]	x[e]	x[e]	x[e]	x[e]		x[e]
BMB/BMA				As clinically indicated														

STUDY 017006: PRETREATMENT, TREATMENT, AND POSTTREATMENT ASSESSMENTS

	Pretreatment Period	Treatment Period									Post-Treatment (Follow-Up, Disease Progression, EOS) Note: efficacy evaluations (CT, PET) not required after PD or subsequent anticancer treatment							
Study Day	**Within 7 days prior to lymphodepletion**	**Lymphodepletion: Ending day -7 to -2[f]**	**1[f]**	**4**	**8**	**11**	**15**	**22**	**29**	**60**	**90**	**180**	**270**	**365**	**455[v]**	**545**	**PD**	**730 (EOS)**
Month	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**	**2**	**3**	**6**	**9**	**12**	**15**	**18**	**N/A**	**24**
Visit Window (days)				± 1	± 1	± 1	± 2	± 2	± 2	± 14	± 14	+ 35	+ 35	+ 35	± 14	± 14	N/A	± 14
AEs/SAEs (9)	AEs/SAEs related to protocol-mandated procedures	Collect all AEs from lymphodepleting chemo to 90 days after JCAR017 treatment[p]											AEs/SAEs related to JCAR017 and/or protocol-mandated procedures[q,r] as well as selected AEs listed in Section 9					
Concomitant Medications (6.5)	Con meds associated with AEs/SAEs related to protocol-mandated procedures	Collect all concomitant meds from lymphodepleting chemo to 90 days after JCAR017 treatment											Concomitant meds ongoing at the time of AEs/SAEs related to JCAR017 and/or protocol-mandated procedures, corticosteroids, GVHD meds, and anticancer therapies					
Anticancer therapies		Throughout study																
Hospitalizations		From first day of lymphodepleting chemotherapy to end of study																

Abbreviations: AE = adverse event; BMA = bone marrow aspirate; BMB = bone marrow biopsy; CNS = central nervous system; CR = complete response CRF = case report form; CSF = cerebrospinal fluid; CT = computed tomography; EOS = end of study; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer – Quality of Life C30 questionnaire; EQ-5D-5L = European Quality of Life-5 Dimensions health state classifier to 5 Levels; ET = early termination; FEV_1 = forced expiratory volume in one second; GVHD = graft-versus-host disease; HCT = hematopoietic cell transplantation; HCT-CI = HCT-specific comorbidity index; IPI = International Prognostic Index; IV = intravenous; LD = lymphodepleting; MMSE = Mini Mental State Examination; MRI = magnetic resonance imaging; MUGA = multigated acquisition; PBMC = peripheral blood mononuclear cells; PCNSL = primary central nervous system lymphoma; PCR = polymerase chain reaction; PD = progressive disease; PET = positron emission tomography; PK = pharmacokinetic; qPCR = quantitative polymerase chain reaction; RCL = replication-competent lentivirus; SCT = stem cell transplantation.

Schedule of Evaluations Footnotes:

a) Serum pregnancy test must be done within 48 hours prior to lymphodepleting conditioning chemotherapy.

b) If a previous tumor biopsy was performed since relapse or since determination of refractory disease, a tumor biopsy will not be required if adequate tissue is available for analysis from the archived sample (see the 017006 laboratory manual for details). For subjects with accessible tumor that receive anticancer treatment for disease control while JCAR017 is being produced, a biopsy must be performed after completion of the intervening anticancer treatment and as close as possible to the start of lymphodepleting chemotherapy (recommended within 7-14 days prior to start).

c) Not required if done at the study site for screening within 6 weeks and no intervening antitumor therapy has been administered. Must be done within 6 weeks prior to the start of lymphodepleting chemotherapy (see Section 8.2.4). If required, recommended within 14 days prior to the start of lymphodepleting chemotherapy. For subjects that receive anticancer treatment for disease control while JCAR017 is being produced, these assessments must be performed after completion of the intervening anticancer treatment and as close as possible to the start of lymphodepleting chemotherapy (recommended within 7-14 days prior to start).

d) If clinically indicated.

e) Required only for subjects with suspected or confirmed CNS involvement, or as clinically indicated.

f) All evaluations and lab assessments must be done prior to administration of lymphodepleting conditioning chemotherapy or JCAR017.

g) To be done on each day of lymphodepleting conditioning chemotherapy.

h) Weight only.

i) Measured within approximately 5 minutes (± 5 minutes) before and 15 minutes (± 5 minutes) after infusion, then approximately every 15 minutes thereafter for the first hour and hourly (± 15 minutes) for the next 2 hours. Continue to monitor vital signs after this point until stable and as clinically indicated.

j) Include routine neurological exam.

k) Obtained anytime from Day 8 to 17; not required for subjects receiving retreatment.

l) PET and CT scan may be performed Day 22 to Day 29.

m) Not done for subjects who have progression/relapse or received subsequent anticancer treatment.

n) Not required if CR previously documented.

o) If more than 1% of cells in test samples collected at the Day 365 visit or later test positive for vector sequences, the pattern of vector integration sites will be analyzed. If a predominant integration site is detected, then the subject will be asked to provide another blood draw 3 months later for follow-up testing.

p) If a subject receives lymphodepleting therapy but not JCAR017, all AE/SAEs should be recorded/reported for 30 days following the last dose of lymphodepleting chemotherapy. For subjects starting a subsequent non-chemotherapy-containing anticancer therapy (eg, checkpoint inhibitors, IMIDs) prior to 90 days following final JCAR017 administration, all AE/SAEs will be collected after initiation of the subsequent therapy for 90 days following final JCAR017 infusion or 30 days following subsequent therapy, whichever is longer. For subjects starting a subsequent chemotherapy-containing anticancer therapy prior to 90 days following final JCAR017 administration, only AEs and SAEs related to JCAR017 and/or protocol-mandated procedures must be recorded/reported after initiation of subsequent therapy.

q) Starting from 91 days after JCAR017 treatment until EOS visit.

r) If any of the following clinical conditions are observed, an SAE should be reported unless the event can be definitely attributed to an alternative cause: second primary malignancies; new onset or exacerbation of a pre-existing neurologic disorder; new onset of a rheumatologic or other autoimmune disorder; new onset of a hematologic disorder; rare and unexpected disorders with an unknown etiology (eg, Guillain-Barré, Stevens-Johnson syndrome).

s) Not required if B-cell recovery documented without recent administration of IVIG.

t) Prior to dose, it must be confirmed that the subject meets criteria for JCAR017 treatment as described in Section 8.2.5.4.

u) Not required for subjects who have received subsequent anticancer treatment.

v) To be performed only for subjects with a first response (CR or PR) documented at the 3-month evaluation.

w) Pregnancy test and contraceptive counseling for females of childbearing potential.

x) If subjects develop neurologic symptoms suspicious of and/or diagnosed as neurologic toxicity, subjects will have daily MMSE exams (see Appendix E) until resolution of symptoms, unless the subject is medically incapacitated and/or medically unable to complete the MMSE. If ICE scores are taken per institutional practice, those scores should be recorded as well.

y) Creatinine clearance (eGFR by Cockcroft-Gault, refer to Appendix C) is required within approximately 48 hours of lymphodepleting chemotherapy to assess the need to adjust the dose of fludarabine.

APPENDIX B. RECOMMENDATIONS FOR INITIAL EVALUATION, STAGING, AND RESPONSE ASSESSMENT OF HODGKIN AND NON-HODGKIN LYMPHOMA: THE LUGANO CLASSIFICATION

The guidelines for Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification are outlined in a report (Cheson 2014).

Table B1: Criteria for Involvement of Site

Tissue Site	Clinical	FDG Avidity	Test	Positive Finding
Lymph nodes	Palpable	FDG-avid histologies Nonavid disease	PET-CT CT	Increase FDG uptake Unexplained node enlargement
Spleen	Palpable	FDG-avid histologies Nonavid disease	PET-CT CT	Diffuse uptake, solitary mass, military lesions, nodules > 13 cm in vertical length, mass, nodules
Liver	Palpable	FDG-avid histologies Nonavid disease	PET-CT CT	Diffuse uptake, mass Nodules
CNS	Signs, symptoms		CT MRI CSF assessment	Mass lesion(s) Leptomeningeal infiltration, mass lesions Cytology, flow cytometry
Other (eg, skin, lung, GI tract, bone, bone marrow)	Site dependent		PET-CT[a], biopsy	Lymphoma involvement

Abbreviations: CNS = central nervous system; CSF = cerebrospinal fluid; CT = computed tomography; FDG = fluorodeoxyglucose; GI = gastrointestinal; MRI = magnetic resonance imaging; PET = positron emission tomography.

[a] PET-CT is adequate for determination of bone marrow involvement and can be considered highly suggestive for involvement of other extralymphatic sites. Biopsy confirmation of those sites can be considered if necessary.

Table B2: Revised Criteria for Response Assessment

Response and Site	PET-CT Based Response	CT-Based Response
Complete	**Complete metabolic response**	**Complete radiologic response (all of the following)**
Lymph nodes and extralymphatic sites	Score 1, 2, or 3[a] with or without a residual mass on 5PS[b] It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (eg, with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake	Target nodes/nodal masses must regress to ≤ 1.5 cm in the longest transverse diameter of a lesion (LDi) No extralymphatic sites of disease
Nonmeasured lesion	Not applicable	Absent
Organ enlargement	Not applicable	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC negative
Partial	**Partial metabolic response**	**Partial remission (all of the following)**
Lymph nodes and extralymphatic sites	Score 4 or 5b with reduced uptake compared with baseline and residual mass(es) of any size At interim, these findings suggest responding disease At end of treatment, these findings indicate residual disease	≥ 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites When a lesion is too small to measure on CT, assign 5 mm × 5 mm as the default value When no longer visible, 0 × 0 mm For a node > 5 mm × 5 mm, but smaller than normal, use actual measurement for calculation
Nonmeasured lesion	Not applicable	Absent/normal, regressed, but no increase
Organ enlargement	Not applicable	Spleen must have regressed > 50% in length beyond normal
New lesions	None	None

Table B2: Revised Criteria for Response Assessment (Continued)

Response and site	PET-CT based response	CT-based response
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan	Not applicable
No response or stable disease	**No metabolic response**	**Stable disease**
Target nodes/nodal masses, extranodal lesions	Score 4 or 5[b] with no significant change in FDG uptake from baseline at interim or end of treatment	< 50% decrease from baseline in SPD of up to 6 dominant measurable nodes and extranodal sites; no criteria for progressive disease are met
Nonmeasured lesion	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	Not applicable
Progressive disease	**Progressive metabolic response**	**Progressive disease requires at least 1 of the following**
Individual target nodes/nodal masses	Score 4 or 5[b] with an increase in intensity of uptake from baseline and/or	PPD progression:
Extranodal lesions	New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	An individual node/lesion must be abnormal with: LDi > 1.5 cm and Increase by ≥ 50% from PPD nadir and An increase in LDi or SDi from nadir 0.5 cm for lesions ≤ 2 cm 1.0 cm for lesions > 2 cm In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (eg, a 15 cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline New or recurrent splenomegaly
Nonmeasured lesions	None	New or clear progression of preexisting nonmeasured lesions

Table B2: Revised Criteria for Response Assessment (Continued)

Response and site	PET-CT based response	CT-based response
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	Regrowth of previously resolved lesions A new node > 1.5 cm in any axis A new extranodal site > 1.0 cm in any axis, if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

Abbreviations: 5PS = 5-point scale; CT = computed tomography; FDG = fluorodeoxyglucose; GI = gastrointestinal; IHC = immunohistochemistry; LDi = longest transverse diameter of a lesion; MRI = magnetic resonance imaging; PET = positron emission tomography; PPD = cross product of the LDi and perpendicular diameter; SDi = shortest axis perpendicular to the LDi; SPD = sum of the product of the perpendicular diameters for multiple lesions.

[a] A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where deescalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid undertreatment).
Measured dominant lesions: Up to 6 of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (eg, liver, spleen, kidneys, and lungs), GI involvement, cutaneous lesions, or those noted on palpation. Nonmeasured lesions: Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites (eg, GI tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response, but should be no higher than surrounding normal physiologic uptake (eg, with marrow activation as a result of chemotherapy or myeloid growth factors).

[b] PET 5PS: 1, no uptake above background; 2, uptake ≤ mediastinum; 3, uptake > mediastinum but ≤ liver; 4, uptake moderately > liver; 5, uptake markedly higher than liver and/or new lesions; X, new areas of uptake unlikely to be related to lymphoma.

Source: Cheson 2014.

APPENDIX C. COCKCROFT-GAULT EQUATION FOR CALCULATING ESTIMATED CREATININE CLEARANCE

Serum creatinine units	Gender	Estimated Creatinine Clearance (mL/min)
mg/dL	Male	$\frac{(140 - \text{subject age [years]}) \times \text{subject weight (kg)}}{72 \times \text{subject serum creatinine (mg/dL)}}$
	Female	$\frac{(140 - \text{subject age [years]}) \times \text{subject weight (kg)} \times 0.85}{72 \times \text{subject serum creatinine (mg/dL)}}$
µM/dL	Male	$\frac{(140 - \text{subject age [years]}) \times \text{subject weight (kg)} \times 1.23}{\text{Subject serum creatinine (µM/dL)}}$
	Female	$\frac{(140 - \text{subject age [years]}) \times \text{subject weight (kg)} \times 1.04}{\text{Subject serum creatinine (µM/dL)}}$

APPENDIX D. MINI MENTAL STATE EXAMINATION

MMSE-2

Standard Version

Blue Form

Date of examination ___/___/___ Examiner _____

Name _____ Age _____ Sex _____

Years of school completed _____ Purpose of exam _____

Assessment of level of consciousness

Alert/ Responsive | Drowsy | Stuporous | Comatose/ Unresponsive

Instructions: Words in boldface type should be read aloud clearly and slowly to the examinee. Item substitutions appear in parentheses. Administration should be conducted privately and in the examinee's primary language. Unless otherwise specified, circle 0 if the response is incorrect or 1 if the response is correct. Begin by introducing the test:

Now I'd like to ask you some questions about your memory.

	RESPONSE	SCORE (circle one)
REGISTRATION		
Listen carefully. I am going to say three words. You say them back after I stop. Ready? Here they are... MILK [*pause*], **SENSIBLE** [*pause*], **BEFORE** [*pause*]. **Now repeat those words back to me.** [*Repeat up to 3 times, but score only the first trial.*]		
MILK		0 1
SENSIBLE		0 1
BEFORE		0 1
Now keep those words in mind. I am going to ask you to say them again in a few minutes.		
ORIENTATION TO TIME		
What day is today? What is the...		
year?		0 1
season?		0 1
month of the year?		0 1
day of the week?		0 1
date?		0 1
ORIENTATION TO PLACE*		
Where are we now? What is the...		
state (or province)?		0 1
county (or city/town)?		0 1
city/town (or part of city/neighborhood)?		0 1
building (name or type)?		0 1
floor of the building (room number or address)?		0 1

*Alternative place words that are appropriate for the setting and increasingly precise may be substituted and noted.

RECALL		
What were those three words I asked you to remember? [*Do not offer any hints.*]		
MILK		0 1
SENSIBLE		0 1
BEFORE		0 1

If administering the MMSE-2:SV, copy the MMSE-2:BV total raw score to the space provided at the top of page 2 and continue with administration.

MMSE-2:BV total raw score ☐ (16 max. points)

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MMSE-2:BV total raw score ☐ (16 max. points)

ATTENTION AND CALCULATION [*Serial 7s*]

Now I'd like you to subtract 7 from 100. Then keep subtracting 7 from each answer until I tell you to stop.

What is 100 take away 7?	[93]	0	1
If needed, say: **Keep going.**	[86]	0	1
If needed, say: **Keep going.**	[79]	0	1
If needed, say: **Keep going.**	[72]	0	1
If needed, say: **Keep going.**	[65]	0	1

Score 1 point for each correct answer. An answer is considered correct if it is 7 less than the previous answer, even if the previous answer was incorrect.

NAMING

What is this? [*Point to eye.*]	0	1
What is this? [*Point to ear.*]	0	1

REPETITION

Now I am going to ask you to repeat what I say. Ready? IT IS A LOVELY, SUNNY DAY BUT TOO WARM. Now you say that. [*Wait for examinee response and record response verbatim. Repeat up to one time.*]

IT IS A LOVELY, SUNNY DAY BUT TOO WARM.	0	1

Detach the last page of this form. Tear the detached page in half along the horizontal perforation line. Use the upper half of the detached page, which has three shapes on it, as a stimulus form for the Comprehension task. Use the bottom half of the page as a stimulus form for the Reading ("CLOSE YOUR EYES") task. Use the upper back half of the detached page as a stimulus and response form for the Drawing (intersecting pentagons) task and the bottom half of the page (blank) as a response form for the Writing task.

COMPREHENSION

Listen carefully because I am going to ask you to do something. [*Show examinee the geometric figures stimulus page.*] **Look at these pictures and point to the circle, then point to the square, and then point to the triangle.**

Correct response	Observed response		
○		0	1
□		0	1
△		0	1

READING

[*Show examinee the word stimulus page.*] **Please do what this says to do.**

CLOSE YOUR EYES	0	1

WRITING

[*Place the blank piece of paper in front of the examinee and provide a pen or pencil.*] **Please write a sentence.** [*If examinee does not respond, say:* **Write about where you live.**] 0 1

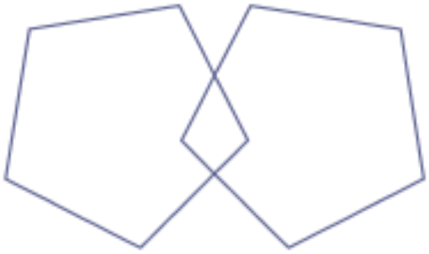
Score 1 point if the sentence is comprehensible and contains a subject and a verb. Ignore errors in grammar or spelling.

DRAWING

[*Display the intersecting pentagons on the stimulus form and provide a pen or pencil.*] **Please copy this design.** Score 1 point if the drawing consists of two 5-sided figures that intersect to form a 4-sided figure. 0 1

MMSE-2:SV total raw score ☐ (30 max. points)

CLOSE YOUR EYES



APPENDIX E. ECOG SCALE

ECOG Status	ECOG Grade
Fully active, able to carry on all pre-disease performance without restriction	0
Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work	1
Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work	1
Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours	2
Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours	2
Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours	3
Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours	3
Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair	4
Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair	4
Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair	4
Dead	5

Adapted from Oken 1982.

APPENDIX F. JCAR017 MANAGEMENT GUIDELINES FOR CYTOKINE RELEASE SYNDROME AND NEUROLOGIC TOXICITIES (V3.02)

1. MANAGEMENT OF TOXICITIES ASSOCIATED WITH JCAR017

Cytokine release syndrome (CRS) and neurologic toxicities (NT) are associated with chimeric antigen receptor (CAR) T cell therapies. Celgene has developed the toxicity management guidelines (TMG) for CRS and NT associated with Celgene cellular products based on current clinical experience across the clinical development programs. These recommendations are based on the CRS revised grading system (Lee, 2014) and the Common Toxicity Criteria for Adverse Events (CTCAE) and need to be used for grading of CRS and NT to guide management in this trial.

If available and adopted as per site standard practice, CRS and NT grading according to the American Society for Transplantation and Cellular Therapy (ASTCT) Consensus Grading System (Lee, 2019) should also be recorded in the case report form (CRF) to inform future modifications of the management guidelines.

2. CYTOKINE RELEASE SYNDROME

Administration of cellular products such as CAR-expressing T cells can be associated with cytokine-associated toxicity due to systemic production and release of various cytokines into the circulation. Cytokine-associated toxicity, also known as CRS, is a toxicity that occurs as a result of immune activation (Lee, 2014; Gardner 2017).

2.1 Pathophysiology of Cytokine Release Syndrome

The hallmark of CRS is immune activation resulting in elevated inflammatory cytokines. Cytokine release syndrome clinically manifests when large numbers of lymphocytes (B cells, T cells, and/or natural killer cells) and/or myeloid cells (macrophages, dendritic cells, and monocytes) become activated and release inflammatory cytokines. Cytokine release syndrome has classically been associated with therapeutic monoclonal antibody (mAb) infusions, most notably anti-CD3 (OKT3), anti-CD52 (alemtuzumab), anti-CD20 (rituximab), and the CD28 super-agonist, TGN1412. Cytokine release syndrome is also frequently observed following administration of bi-specific T cell engaging antibodies for leukemia, and adoptive cellular immunotherapies for cancer, most notably CAR T cells. Incidence, time to onset and severity of CRS due to CAR T cells is at least partially dependent on the infused cell dose and tumor burden/antigen density, presumably due to more rapid and higher levels of CAR T cell activation. Onset of CRS symptoms typically occurs days to occasionally weeks after the CAR T cell infusion, usually preceding maximal in vivo T cell expansion. Cytokine release syndrome is associated with elevated interferon gamma (IFNγ), interleukin (IL)-6, and tumor necrosis alpha (TNF-α) levels, and increases in IL-2, granulocyte macrophage colony-stimulating factor (GM-CSF), IL-10, IL-8, IL-5, and fractalkine although the pattern of elevated cytokines varies among subjects (Davila 2014; Hay 2017). IL-6 has been identified as a central mediator of toxicity in CRS. IL-6 is a pleiotropic cytokine with anti-inflammatory and proinflammatory properties. High levels of IL-6, present in the context of CRS, likely initiates a proinflammatory IL-6-mediated signaling cascade.

2.2 Clinical Presentation of Cytokine Release Syndrome

Cytokine release syndrome is characterized by high fever, fatigue, nausea, headache, dyspnea, tachycardia, rigors, hypotension, hypoxia, myalgia/arthralgia, and anorexia. Clinical symptoms and severity of CRS are highly variable (Lee 2014), and management can be complicated by concurrent conditions. In non-Hodgkin lymphoma (NHL) subjects treated with JCAR017, CRS usually occurs within two weeks after infusion (Abramson 2017).

- Fever, especially high fever (≥ 38.5°C or ≥ 101.3°F), is a commonly-observed hallmark of CRS, and many features of CRS mimic infection. Hence, infection must be considered in all subjects presenting with CRS symptoms, and appropriate cultures must be obtained and empiric antibiotic therapy initiated per institution standard of care.
- Less common symptoms associated with CRS include cardiac dysfunction, adult respiratory distress syndrome, renal and/or hepatic failure, coagulopathies, disseminated intravascular coagulation, and capillary leak syndrome.
- Neurologic toxicity has been observed concurrently with CRS; refer to Section 4.
- CRS has been reported in some cases to be associated with findings of macrophage activation syndrome (MAS)/hemophagocytic lymphohistiocytosis (HLH), and the physiology of the syndromes may overlap; refer to Section 3 of this appendix.

2.3 Clinical Management of Cytokine Release Syndrome

Across various CD19 CAR T cell products, early manifestations of CRS can predict more severe toxicity for both CRS and NT.

Subjects with B-cell acute lymphoblastic leukemia (ALL) and high burden of disease are at high risk of developing CRS (Frey 2017). Subjects with NHL who have high baseline tumor burden (measured by the sum of product of the perpendicular diameters [SPD] or high serum lactate dehydrogenase [LDH; ≥ 500 U/L] prior to the start of lymphodepletion) also have a higher risk for developing CRS and/or neurotoxicity (Siddiqi 2017).

High baseline levels of other commonly measured inflammatory markers, such as ferritin and C-reactive protein (CRP), were also associated with CRS.

It should be noted that, although useful for identifying subjects at higher risk for developing CRS, CRP, ferritin, and serum cytokine levels should not be used for CRS clinical management/treatment decisions in the absence of other clinical signs and symptoms of CRS; for example, a subject with an elevated CRP but no concomitant symptoms may not require intervention (Park 2017). Thus, close observation of these subjects is strongly recommended.

A modification of the CTCAE CRS grading scale has been established to better reflect CAR T cell-associated CRS, as detailed in Table 10 (Lee 2014).

Table 10: Grading Criteria for Cytokine Release Syndrome

	Symptoms/Signs	Cytokine Release Syndrome (CRS) Grade 1 (mild)	CRS Grade 2 (moderate)	CRS Grade 3 (severe)	CRS Grade 4 (life-threatening)
			CRS grade is defined by the most severe symptom (excluding fever)		
Vital Signs	Temperature ≥ 38.5°C/101.3°F	Yes	Any	Any	Any
	Systolic blood pressure (SBP) ≤ 90 mmHg	N/A	Responds to intravenous (IV) fluids or single low-dose vasopressor[a]	Needs high-dose[a] or multiple vasopressors	Life-threatening
	Need for oxygen to reach oxygen saturation (SaO_2) > 90%	N/A	Fraction of inspired oxygen (FiO_2) < 40%	$FiO_2 \geq 40\%$	Needs ventilator support
Organ Toxicity		N/A	Grade 2	Grade 3 or transaminitis Grade 4	Grade 4 (excluding transaminitis)

[a] Definition of high-dose vasopressors in Table 11.

Table 11: High Dose Vasopressors (all doses required for ≥ 3 hours)

Vasopressor	Dose
Norepinephrine monotherapy	≥ 20 µg/min
Dopamine monotherapy	≥ 10 µg/kg/min
Phenylephrine monotherapy	≥ 200 µg/min
Epinephrine monotherapy	≥ 10 µg/min
If on vasopressin	Vasopressin + norepinephrine equivalent (NE) of ≥ 10 µg/min[a]
If on combination vasopressors (not vasopressin)	Norepinephrine equivalent of ≥ 20 µg/min[a]

[a] VASST Trial Vasopressor Equivalent Equation: Norepinephrine equivalent dose = [norepinephrine (µg/min)] + [dopamine (µg/kg/min) ÷ 2] + [epinephrine (µg/min)] + [phenylephrine (µg/min) ÷ 10].
Adapted from (Lee 2014).

Detailed CRS management guidelines are shown in Figure 1. Treatment should be individualized for each subject's clinical needs. This guidance emphasizes the importance of early intervention for Grade 2 CRS, or in the setting of a rapid onset or rapid progression of CRS symptoms, to prevent the development of severe (Grade 3 or greater) CRS and neurotoxicity.

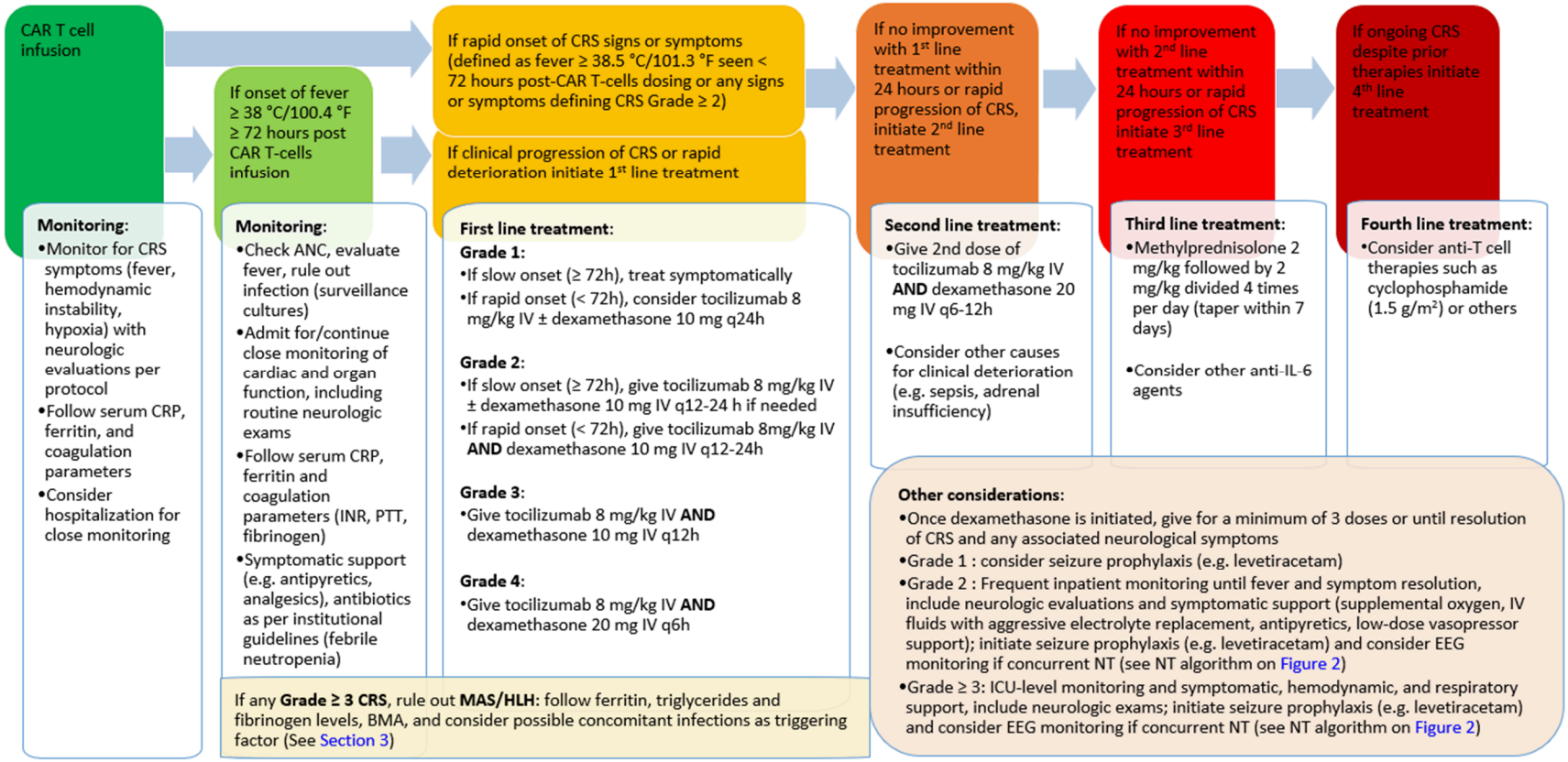
In some cases, tocilizumab, an anti-IL-6R-antibody, may be required to treat toxicities such as severe CRS. Please refer to the currently approved Actemra® prescribing information (US) or RoActemra® Summary of Product Characteristics (EU). Actemra® has been approved by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for the

treatment of CAR T cell-induced severe or life-threatening CRS in adults. The preferred dose to intervene in adult subjects with CRS is 8 mg/kg (maximum 800 mg) IV. If no clinical improvement in the signs and symptoms of CRS occurs after the first dose, additional doses of tocilizumab may be administered (please see Figure 1, Actemra® prescribing information (US) and Summary of Product Characteristics (EU).

Other anti-IL-6 agents, if available in the country, should be considered in the event of severe CRS not responding to tocilizumab and corticosteroids. Dosing of any other anti-IL-6 agent should be per prescribing information.

In the most unresponsive severe cases additional treatments with T cell depleting therapies such as cyclophosphamide should be considered (Brudno 2016).

Figure 1: JCAR017 Cytokine Release Syndrome Treatment Algorithm



ANC = absolute neutrophil count; BMA = bone marrow aspirate; CAR = chimeric antigen receptor; CRP = C-reactive protein; CRS = cytokine release syndrome; EEG = electroencephalogram; HLH = hemophagocytic lympho-histiocytosis; ICU = intensive care unit; IL-6 = interleukin 6; INR = international normalized ratio; IV = intravenous; MAS = macrophage activation syndrome; NT = neurotoxicity; PTT = partial thromboplastin time; q = every.

3. MACROPHAGE ACTIVATION SYNDROME /HEMOPHAGOCYTIC LYMPHO-HISTIOCYTOSIS

Macrophage activation syndrome (MAS) or HLH is a rare, potentially fatal immune-mediated disease, which is caused by impaired natural killer and cytotoxic T-cell function. This syndrome has a wide range of causes, symptoms, and outcomes, but all lead to a hyperinflammatory response (with some characteristics that overlap with CRS and organ damage (Ramos-Casals, 2014). Cases of MAS/HLH have been described in patients treated with CAR T-cell therapies (Neelapu, 2017).

3.1 Pathophysiology of Macrophage Activation Syndrome/Hemophagocytic Lymphohistiocytosis

Macrophage activation syndrome/hemophagocytic lymphohistiocytosis is divided into primary (genetic) and secondary (reactive) forms. Secondary MAS/HLH is subclassified as viral, autoimmune, or tumor related. MAS/HLH has both infectious and non-infectious triggers (Ramos-Casals, 2014). Viral infection is the most frequent trigger, either due to primary infection or after reactivation in immunosuppressed patients. Bacterial and fungal infections can also trigger MAS/HLH. Macrophage activation like syndrome (MALS) is a distinct entity that leads to early death in septic patients and must be carefully ruled out in patients who are prone to develop severe infections, including patients following CAR T-cell therapy (Karakike, 2019). Patients with hematological malignancies, in particular lymphoma, have a higher risk of developing MAS/HLH.

3.2 Clinical Presentation and Diagnosis of Macrophage Activation Syndrome/Hemophagocytic Lymphohistiocytosis

The presentation of secondary MAS/HLH is heterogeneous and characterized by a panoply of clinical signs and symptoms. The clinical syndrome can be acute or subacute with non-specific symptoms appearing over few days to 4 week(s) (Ramos-Casals, 2014). The cardinal features are continuous high fever (≥ 38.5°C) and enlarged lymphohematopoietic organs (spleno/hepatomegaly, occasionally accompanied by adenopathy). Pulmonary, neurologic, cutaneous and gastrointestinal involvement may also be present.

Laboratory markers associated with MAS/HLH include pancytopenia, hyperferritinemia, hypofibrinogenemia and raised D-dimer levels, hypertriglyceridemia, and abnormalities in liver function.

Detection of any ongoing infection acting as a trigger for MAS/HLH is critical (Figure 1). Standard tests should be used to screen for infections caused by the most common viruses such as herpes, cytomegalovirus (CMV) and Epstein-Barr virus (EBV). Other infectious agents (eg, mycobacteria, parasites, and fungi, particularly Candida and Mucor) should be ruled out according to specific clinical or epidemiological features (Ramos-Casals, 2014; Lehmberg, 2015).

Bone marrow is the preferred anatomical site for investigation of suspected MAS/HLH. Bone marrow aspirate can be negative at the initial stage of MAS/HLH and should be repeated during the clinical course if there is a high suspicion of MAS/HLH.

The diagnosis of MAS/HLH (according to HLH-2004 consensus criteria, further revised in 2014 for HLH associated with malignancies) (Lehmberg, 2015) can be established if either of the two criteria below is fulfilled:

1. A molecular diagnosis consistent with MAS/HLH
2. Diagnostic criteria for MAS/HLH fulfilled (five out of the eight criteria below):
    - High persistent fever (≥ 38.5°C)
    - Splenomegaly
    - Cytopenias (affecting 2 of 3 lineages in the peripheral blood): Hemoglobin < 90 g/L, platelets < 100×10^9/L, neutrophils < 1.0×10^9/L
    - Triglycerides ≥ 3.0 mmol/L (ie, 265 mg/dL) or fibrinogen ≤ 1.5 g/L
    - Hemophagocytosis in bone marrow, spleen and/or lymph nodes
    - Low or absent NK-cell activity (according to local laboratory reference)
    - Ferritin ≥ 500 ng/mL
    - Soluble CD25 (ie, soluble IL-2 receptor) ≥ 2,400 U/mL

3.3 Clinical Management of Macrophage Activation Syndrome/Hemophagocytic Lymphohistiocytosis

Effective treatment of MAS/HLH requires multiple simultaneous approaches (Ramos-Casals, 2014; Lehmberg, 2015).

1. Supportive care is essential because of frequent life-threatening severe manifestations at presentation.

2. The elimination of triggers (particularly infection) is crucial to remove the stimuli that initiate the abnormal immune system activation. Appropriate broad-spectrum antiviral, antibacterial, antifungal prophylaxis and treatment must be initiated.

3. Suppression of the inflammatory response and cell proliferation by immunosuppressive and cytotoxic drugs, respectively, is necessary. First line treatment includes IL-6-blockade with tocilizumab. Glucocorticoids are also indicated for the initial treatment of MAS/HLH, irrespective of the cause (CRS Grade 4 treatment recommendations should be followed). IL-1 blockade with anakinra is suggested as second line treatment or in case of rapidly progressing clinical course. Anti-IL-6 antibody siltuximab might be considered as well as second line therapy. The use of cyclosporin, cyclophosphamide, etoposide and/or intrathecal methotrexate is not generally indicated in patients who develop MAS/HLH after CAR T-cell therapy, but may have to be employed in refractory cases.

Newer emerging treatments include emapalumab (anti IFN-gamma antibody), which has been approved by FDA for the treatment of primary refractory or recurrent MAS/HLH (Benedetti, 2019).

4. NEUROLOGIC TOXICITIES

CAR T cell therapy is associated with unique neurologic toxicities. Neurologic symptoms may include altered mental status, aphasia, altered level of consciousness, and seizures or seizure-like activity. With JCAR017, to date, the start of neurologic symptoms has been noted between 3 to 23 days (median 10 days) (Abramson 2017) after CAR T cell infusion and in severe cases may require admission to the intensive care unit (ICU) for frequent monitoring, respiratory support, or intubation for airway protection. The symptoms are variable and generally occur as CRS is resolving or after CRS resolution.

4.1 Pathophysiology of Neurologic Toxicities

The pathogenesis of neurotoxicity is poorly defined. Analysis of a subset of subjects treated with JCAR017 (study 017001 – TRANSCEND NHL001) with NHL who have high baseline tumor burden (measured by the sum of product of the perpendicular diameters or high serum LDH (≥ 500 U/L) prior to the start of lymphodepletion) also have a higher risk for developing neurotoxicity (Siddiqi 2017). In addition, severe neurotoxicity has also been reported in subjects with B-cell ALL and higher disease burden at the time of CD19 directed CAR T cell infusion (Park 2017; Gust 2017).

Peak levels of IL-6, IFN-γ, ferritin, and CRP are significantly higher in subjects who develop any grade or Grade 3 or higher neurotoxicity (Turtle 2016; Heipel 2017). Protein levels in the cerebrospinal fluid (CSF) are usually elevated in patients with neurotoxicity, compared with baseline measurements, suggesting disruption of the blood-brain barrier. Other organ dysfunction (hepatic and renal), as well as hypoxemia, and infection, might also contribute to the encephalopathy (Neelapu 2018). In another study, it has been reported that evidence for cytokine-mediated endothelial activation causes coagulopathy, capillary leak, and blood-brain barrier disruption allowing transit of high concentrations of systemic cytokines into the CSF (Gust 2017).

4.2 Clinical Management of Neurologic Toxicities

The optimal management of CAR T cell-induced neurotoxicity is unknown at this time. These management guidelines represent the current state of knowledge and additional information will be provided to Investigators as it becomes available. Management should also be guided as per institutional or standard clinical practice, and as determined by the Investigator or treating physician and/or consulting neurologist. A thorough neurologic evaluation, including electroencephalogram (EEG), magnetic resonance imaging (MRI) or computer tomography (CT) scan of the brain and diagnostic lumbar puncture and frequent monitoring of cognitive function (eg, mini mental status exams or handwriting tests) should be considered.

Treatable causes of neurologic dysfunction, such as infection or hemorrhage should be ruled out. Common manifestations of neurotoxicity (eg, confusion, seizure, aphasia), can also be seen with infection, electrolyte imbalances, metabolic acidosis, uremia, concomitant medication use (eg, narcotics), and other medical conditions. Other causes for such symptoms should be considered.

Magnetic resonance imaging and CT scans of the brain are usually negative for any anatomical pathology that would account for the neurotoxicity symptoms observed in subjects treated with CAR T cell therapy, although rare cases of reversible T2/fluid attenuated inversion recovery

(FLAIR) MRI hyperintensity involving the thalami, dorsal pons, and medulla, and cerebral edema have been reported (Neelapu 2018).

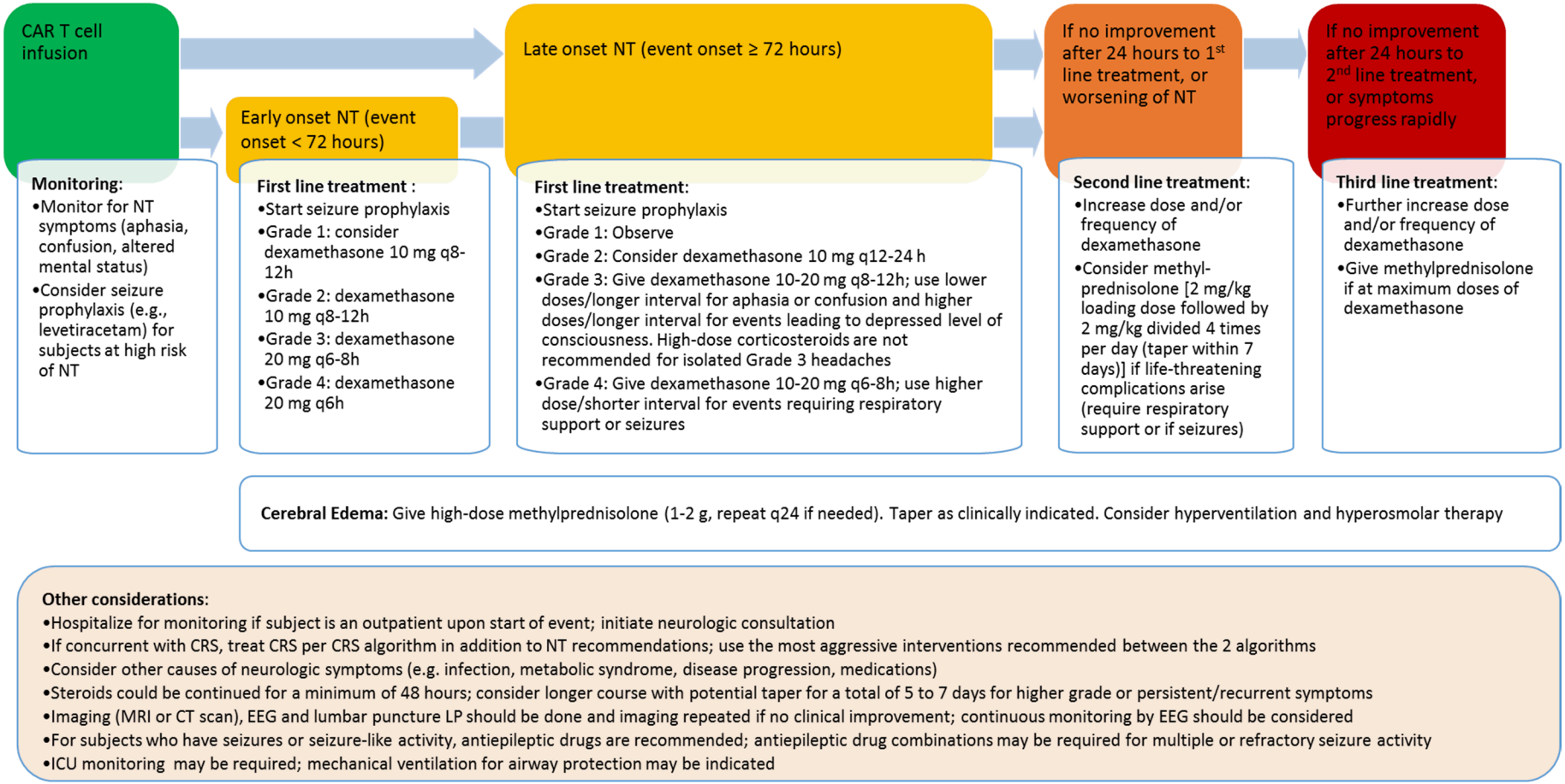
For subjects who have neurologic toxicity in the presence of CRS, the CRS should be managed following the guidelines provided in Figure 1.

Neurotoxicity should be evaluated following the guidelines provided in Figure 2. For concurrent CRS and neurotoxicity, the most aggressive intervention recommended by either guideline should be employed (if the recommendations for steroid doses differ, use the highest dose and/or frequency). For subjects with Grade 4 neurotoxicity with cerebral edema, high-dose corticosteroids, hyperventilation and hyperosmolar therapy has been recommended (Neelapu 2018).

Note: Tocilizumab is not recommended for the treatment of neurotoxicity related to CAR T cell therapy, unless CRS or MAS/HLH is also present. Results from 2 studies, one of preemptive use of tocilizumab shortly after anti-CD19 CAR T cell therapy in relapsed/refractory NHL subjects (Locke 2017), and the other mandatory use of tocilizumab at first fever [> 38.5 °C] in pediatric ALL patients treated with anti-CD19 CAR T cells (Gardner 2017), demonstrated that early tocilizumab use either increased overall neurotoxicity and Grade ≥ 3 neurotoxicity rates (85% vs 62% overall; 35% vs 26% Grade ≥ 3) or provided no improvement in neurotoxicity rates, respectively. These findings support the hypothesis that tocilizumab does not improve and may worsen isolated neurotoxicity (Locke 2017).

Neurotoxicity management guidelines are provided in Figure 2.

Figure 2: Neurotoxicity Treatment Algorithm



Abbreviations: CAR = chimeric antigen receptor; CRS = cytokine release syndrome; CT = computed tomography; EEG = electroencephalogram; ICU = intensive care unit; LP = lumbar puncture; MRI = magnetic resonance imaging; NT = neurotoxicity; q = every.

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APPENDIX G. CAIRO-BISHOP DEFINITIONS OF TUMOR LYSIS SYNDROME

Cairo-Bishop Definition of Laboratory Tumor Lysis Syndrome (LTLS)

Laboratory Parameter	Laboratory Result
Uric acid	≥ 476 µmol/L (≥ 8.0 mg/dL) or 25% increase from baseline
Potassium	≥ 6.0 mmol/L (≥ 6.0 mEq/L) or 25% increase from baseline
Phosphorous	≥ 1.45 mmol/L (≥ 4.5 mg/dL) or 25% increase from baseline
Calcium	≤ 1.75 mmol/L (≤ 7.0 mg/dL) or 25% decrease from baseline

Laboratory tumor lysis syndrome (LTLS) is defined as either a 25% change or level above or below normal, as defined above, for any two or more serum values of uric acid, potassium, phosphate, and calcium within 3 days before or 7 days after the initiation of chemotherapy. This assessment assumes that a patient has or will receive adequate hydration (± alkalinization) and a hypouricaemic agent(s).

Cairo-Bishop Definition of Clinical TLS

The presence of laboratory TLS and one or more of the following criteria:
1. Creatinine: ≥ 1.5 ULN (age > 12 years or age adjusted)
2. Cardiac arrhythmia/sudden death[a]
3. Seizure[a]

Abbreviations: TLS = tumor lysis syndrome; ULN = upper limit of normal.
[a] Not directly attributable to a therapeutic agent.

Cairo-Bishop Grading System for TLS

Grade	LTLS	Creatinine	Cardiac Arrhythmia	Seizure
0	-	≤ 1.5 × ULN	None	None
1	+	1.5 × ULN	Intervention not indicated	None
2	+	> 1.5 – 3.0 × ULN	Non-urgent medical intervention indicated	One brief generalized seizure; seizure(s) well controlled or infrequent; focal motor seizures not interfering with activities of daily life (ADL)

Cairo-Bishop Grading System for TLS (Continued)

Grade	LTLS	Creatinine	Cardiac Arrhythmia	Seizure
3	+	> 3.0 – 6.0 × ULN	Symptomatic and incompletely controlled medically or controlled with device	Seizure in which consciousness is altered; poorly controlled seizure disorder; breakthrough generalized seizures despite medical intervention
4	+	> 6.0 × ULN	Life-threatening	Seizures of any kind that are prolonged, repetitive, or difficult to control
5	+	Death[a]	Death[a]	Death[a]

Abbreviations: ADL = activities of daily living; LTLS = laboratory tumor lysis syndrome; TLS = tumor lysis syndrome; ULN = upper limit of normal.
[a] Probably or definitely attributable to clinical TLS.
Source: Cairo, 2004.

Celgene Signing Page

This is a representation of an electronic record that was signed electronically in Livelink. This page is the manifestation of the electronic signature(s) used in compliance with the organizations electronic signature policies and procedures.

UserName: [redacted]
Title: [redacted]
Date: Wednesday, 18 August 2021, 10:40 AM Eastern Daylight Time
Meaning: Approved, no changes necessary.
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1. JUSTIFICATION FOR AMENDMENT

Significant changes included in this amendment are summarized below:

Statistical Methods

- **Specified that a formal hypothesis testing will occur at the time of the primary analysis for the study**

[redacted] a formal hypothesis testing will be performed on the 017006 dataset instead of the pooled analysis set (Study 017006 [PILOT] and JCAR017-BCM-001 Cohort 2 combined).

Revised sections: Protocol Synopsis, Section 10.3.2 Primary Endpoint, Section 10.5, Sample Size considerations, Section 10.6.1, Primary Analysis

Timing of Analyses

- **Study 017006 primary analysis will be triggered when approximately 62 subjects treated with JCAR017 have been followed for at least 6 months**

[redacted] the timing of the primary efficacy analysis was amended to occur after approximately 62 treated patients have been followed for at least 6 months after first response. It was also clarified that additional efficacy analyses may be performed per health authorities' requests without any intention for hypothesis testing or change of study conduct.

Revised sections: Section 10.6, Timing of Analyses, Section 10.6.1 Primary Analysis

Study Assessments (Research Samples)

- **Updated serious adverse event (SAE) reporting requirement for clonal outgrowth or monoclonality from vector site insertion**

Requirement to report clonal outgrowth or monoclonality from vector site insertion as an SAE was removed because the occurrence of clonal outgrowth will not result in a malignancy. All subjects will be closely monitored for signs of malignancy [redacted]. In the event of a secondary primary malignancy (SPM), a sample of the neoplastic tissue will be requested for causality analysis related to use of integrating vector to determine if insertional oncogenesis is suspected.

Revised sections: Section 7.12, Replication-Competent Lentivirus, Clonality, and Insertional Oncogenesis, Section 8.3.9.3, Viral Vector Sequence Testing

The amendment also includes the following minor clarifications and corrections:

- Updated contact information of Medical Director
- Updated wording on U.S. Food & Drug Administration (FDA) approved CD19-directed chimeric antigen receptor (CAR) T cell therapies to reflect liso-cel approval (Section 1.3)

- Updated study objectives and endpoints (Table 2)
- Clarified the rationale for using the reference rate for the null hypothesis provided by Real-World Evidence (RWE) study for testing the primary endpoint of overall response rate (ORR) (Section 10.3.2)
- Added wording on coronavirus disease 2019 (COVID-19) adverse events (AEs) and COVID-19-related protocol deviations reporting (Section 10.3.6.1, Section 11.5)
- Updated software used to calculate sample size and power from nQuery® 7.0 to EAST v6.4.1 (Protocol Synopsis, Section 10.5)
- Changes to subgroup analyses (Section 10.3.4)
  - Added additional subgroup analyses under prior response status to front-line therapy, including:
    - Refractory (best overall response [BOR] to front-line therapy of progressive disease [PD)/stable disease [SD]/partial response [PR]) or complete response (CR) lasting < 3 months versus CR lasting ≥ 3 months and ≤ 12 months
    - Chemorefractory (BOR to front-line therapy of PD/SD) versus chemosensitive (BOR of CR/PR)
  - Added additional subgroup analysis of Eastern Cooperative Oncology Group (ECOG) score 0 to 1 versus 2
  - Added additional subgroup analyses of bridging anticancer therapy for disease control:
    - Yes versus No
    - Platinum-based regimen versus non-platinum-based regimen versus no bridging regimen
  - Added additional subgroup analysis of NHL subtype: Diffuse large B-cell lymphoma (DLBCL), not otherwise specified (NOS), high-grade B-cell lymphoma (HGL), transformed follicular lymphoma (tFL), follicular lymphoma Grade 3B (FL3B)
  - Added additional subgroup analysis with subgroups defined by age/organ function and disease status
  - Clarified sum of the product of the perpendicular diameters (SPD) per Independent Review Committee (IRC) at pre-lymphodepleting chemotherapy (LDC) subgroup analysis will be evaluating SPD < 50 cm2 versus ≥ 50 cm2
  - Clarified lactate dehydrogenase (LDH) at pre-LDC subgroup analysis will be evaluating LDH < 500 U/L versus ≥ 500 U/L
  - Clarified screening hematopoietic cell transplantation-specific comorbidity index (HCT-CI) score will be used for HCT-CI score ≥ 3 versus < 3 subgroup analysis
- Updated References section (Section 13)

- Corrected misspellings, style, and formatting throughout

1. JUSTIFICATION FOR AMENDMENT

Significant changes included in this amendment are summarized below:

Statistical Methods

- **Details regarding the pooled efficacy analysis of overall response rate (ORR) have been removed throughout the protocol**

This analysis will still be performed. However, the details of the analysis will be presented in a separate statistical analysis plan (SAP), and the results of the analysis will be presented in a different document than the 017006 Clinical Study Report (CSR), since the analysis will utilize pooled data from 017006 and BCM-001 Cohort 2.

Revised sections: Protocol Synopsis, Section 10 Statistical Methods, Section 10.3.2 Primary Endpoint, Section 10.5 Sample Size Considerations

- **Specified efficacy information for subjects enrolled in Study 017006 will be summarized using descriptive statistics without formal hypothesis testing**

Hypothesis testing for the primary efficacy endpoint of ORR will be performed on the pooled analysis set only. Descriptive statistics of ORR will be provided for 017006 itself without hypothesis testing.

Revised sections: Protocol Synopsis, Section 10.1 General Considerations, Section 10.3.2 Primary Endpoint

Timing of Analyses

- **Study 017006 primary analysis will be triggered when last enrolled subject treated with JCAR017 has been followed for at least 1 postbaseline assessment instead of 6 months**

The primary efficacy analysis is on overall response rate, which does not require 6 months of follow up to determine. All patients will be followed for efficacy for 2 years or until death, disease progression, or withdrawal from study, and the results summarized at the time of final analysis.

Revised sections: Section 10.6.1 Primary Analysis

Sample Size

- **Increase in total sample size from at least 56 to approximately 62 JCAR017-treated subjects on the 017006 study**

The hypothesis-testing pooled analysis will be based on a sample size of 80 patients from Study 017006 and BCM-001 Cohort 2. This change to the Study 017006 sample size allows flexibility in the number of patients included from each study.

Revised sections: Protocol Synopsis and Section 10.5 Sample Size Considerations

The amendment also includes several other minor clarifications and corrections:

- New Study Manager contact information added
- Updated email address of Medical Director, Medical Monitor, and Statistician from @junotherapeutics.com address to @bms.com address

- Title of Statistician updated
- Clarified that safety data will be summarized based on the JCAR017-treated Analysis Set (Protocol Synopsis)
- Updated the terms "chart review" and "historical control" to "patient-level real-world data cohort" and "external control" respectively, to more accurately describe the generation of the null hypothesis (Protocol Synopsis, Section 1.1, Section 10.3.2, Section 10.5)
- Updated the total time from first subject first visit for all subjects to complete the study from approximately 3 years to approximately 4 years (Protocol Synopsis and Section 4.2)
- Clarified language regarding performing and capturing Immune Effector Cell-Associated Encephalopathy (ICE) scores coupled with other neurological assessments (Section 8.2.4, Section 8.2.5.5, Section 8.2.7, Section 8.3.3, Appendix A)
- Clarified that post-retreatment data from subjects who received retreatment of JCAR017 will be summarized separately from subjects treated once (Section 10.1)
- Updated wording of the JCAR017-treated Analysis set (Section 10.2.4)
- Removed use of the word "conforming" throughout the protocol (Section 10.2.4, Section 10.2.6)
- Updated the Pharmacokinetic Analysis Set to include quantitative polymerase chain reaction (qPCR) and Flow Cytometry subsets (Section 10.2.7)
- Added additional analysis set of Patient-reported Outcome Analysis Set (Section 10.2.8)
- Clarified best overall response definition to not include responses from retreatment with JCAR017 (Section 10.3.2)
- Updated definition of refractory status from less than complete response (CR) to last prior therapy to less than CR to frontline therapy (Section 10.3.4)
- Changes to subgroup analyses
  - Added < 70 versus ≥ 70 cutoffs to the age subgroup analysis (Section 10.3.4)
  - Added additional subgroup analysis of prior response status to frontline therapy: Refractory disease or relapsed disease ≤ 12 months (defined as CR lasting no more than 12 months) versus relapsed disease later than 12 months (defined as CR lasting more than 12 months (Section 10.3.4)
  - Added additional subgroup analysis of hematopoietic cell transplant specific comorbidity index (HCT-CI) score: ≥ 3 versus < 3 (Section 10.3.4)
  - Added additional subgroup analysis of age adjusted International Prognostic Index (IPI) (aaIPI) score: ≥ 2 versus ≤ 1 (Section 10.3.4)

  - Added additional subgroup analysis of sum of the products of the perpendicular diameters (SPD) per independent review committee (IRC) at pre-lymphodepleting chemotherapy (LDC) (Section 10.3.4)
  - Added additional subgroup analysis of lactate dehydrogenase (LDH) at pre-LDC (Section 10.3.4)
- Removed subgroup analysis of prior chemotherapy response status: chemorefractory versus chemosensitive to frontline therapy as all subjects received chemotherapy first line (Section 10.3.4)
- Clarified definition of treatment-emergent adverse event (TEAE) (Section 10.3.6.1)
- Added clarifying language to the Final Analysis section (Section 10.6.2)
- Corrected footnote error under procedure column for positron emission tomography (PET) and computed tomography (CT) scans in Schedule of Evaluations (Appendix A)
- Clarified circumstances under which PET and CT scans are not required to be repeated at pretreatment (Appendix A)
- Abbreviations added to List of Abbreviations
- Corrected misspellings, style, and formatting throughout

1. JUSTIFICATION FOR AMENDMENT

Significant changes included in this amendment are summarized below:

Study Assessments

- **Added guidance that if subjects develop neurologic toxicity, daily Mini Mental Status Exam (MMSE) evaluations should be conducted until resolution of symptoms**

  Following the publication of the American Society for Transplantation and Cellular Therapy (ASTCT) Consensus Grading for Cytokine Release Syndrome and Neurological Toxicity Associated with Immune Effector Cells in 2018, discrepancies in neurotoxicity assessment emerged between current JCAR017 protocols and the new ASTCT guidelines. In order to adequately capture all factors required to assess neurotoxicity per the new ASTCT guidelines, daily MMSE assessments throughout the duration of neurotoxicity events are now required.

  Also included information on collection of grading according to American Society for Transplantation and Cellular Therapy (ASTCT) Consensus Grading System.

  Revised Sections: Section 7 Potential Risks and Management of Toxicities, Section 8.2.7 Unscheduled Evaluations, 8.3.3 Mini Mental State Examinations, Appendix A Schedules of Evaluations

Study Population

- **Revised exclusion criteria regarding tumor invasion of vessels and deep venous thrombosis (DVT)/pulmonary embolism (PE) following recommendation from data safety monitoring committee**

  The exclusion criteria that are being modified were originally added in consultation with the JCAR017 Data Safety Monitoring Board (DSMB) after review of an Urgent Safety Measure regarding the death of a subject in study JCAR017-BCM-001, a global Phase 1/2 study of JCAR017 in relapsing/refractory third-line aggressive B-cell lymphoma. Additional details regarding the fatal case on JCAR017-BCM-001 suggested that the medical history of DVT and PE, the therapeutic anticoagulation, and the vascular invasion by tumor, were not related to the cause of death from candida sepsis and respiratory failure from candida pneumonia seen at autopsy. The subsequent removal of these criteria was supported by the same DSMB based on an analysis of subjects with a medical history of DVT/PE and/or anticoagulation use in the 017001 (TRANSCEND NHL 001) study showing there was no increase of bleeding events or fatal events related to DVT, PE, or anticoagulation in patients on therapeutic anticoagulation or a medical history of DVT/PE, respectively. Thus, the exclusion criterihave been revised to only exclude patients with venous thrombosis or embolism not managed on a stable regimen of anticoagulation or patients with progressive vascular tumor invasion, thrombosis, or embolism.

  Revised Sections: Protocol Synopsis, Section 5.2 Exclusion Criteria, Section 8.2.5.3 Criteria for JCAR017 Treatment

This amendment also includes several other minor clarifications and corrections:

- Protocol title page updated to include 017006 Medical Monitor mailbox email and reflect updated study personnel
- Reordered secondary objectives and endpoints so all efficacy endpoints are noted together (Protocol Synopsis, Section 3, Section 10.3.3)
- Clarified exclusion criterion of active hepatitis B and hepatitis C (Protocol Synopsis, Section 5.2)
- Updated contraception requirements, lactation, and pregnancy language in Inclusion Criteria and Exclusion Criteria to align with program-wide changes. Pregnancy tests and contraceptive counseling for females of childbearing potential were also added at study visits every 3 months until 12 months after lymphodepleting chemotherapy (LDC) (Protocol Synopsis, Section 5.1, Section 5.2, Section 9.4.6, Section 9.5, Appendix A. Previous Section 5.3 removed.)
- Added more detail regarding safety analyses, including more detail on adverse events of special interest (AESIs) to be analyzed (Protocol Synopsis, Section 10.3.6.1)
- Updated information on approved CAR T-cell products and clinical experience with JCAR017 (Section 1.3, Section 1.4, Section 1.5)
- Added death as a possible reason for subject discontinuation prior to receiving study treatment (Section 5.3.2 [previously Section 5.4.2])
- Updated JCAR017 preparation and administration section to include the option of an on-site liquid nitrogen freezer for storage (Section 6.2.2)
- Updated Nonconforming Product language, including reference to the Protocol Product Deviation Plan and clarified exceptions for use (Section 6.2.3)
- To align with JCAR017 program protocols, moved language describing tocilizumab use for management for cytokine release syndrome from the section on JCAR017 Management Guidelines for Cytokine Release Syndrome and Neurotoxicity to the section on Recommended Supportive Care, Additional Treatment, and Monitoring (Section 6.4, Appendix F)
- Clarified language in the prohibited concomitant medications section, and specified that immunosuppressive medications are prohibited (Section 6.6)
- Added guidance that, if available and adopted as per site standard practice, cytokine release syndrome (CRS) and neurotoxicity (NT) grading according to the American Society for Transplantation and Cellular Therapy (ASTCT) Consensus Grading System should also be recorded in the case report form (CRF) to inform future modifications of the management guidelines (Section 7 and Section 7.1)
- Added that tocilizumab is not recommended for treatment of neurologic toxicities unless CRS or macrophage activation syndrome (MAS)/hemophagocytic lymphohistiocytosis (HLH) is also present (Section 7.5)

- Updated the JCAR017 Management Guidelines for Cytokine Release Syndrome and Neurologic Toxicities to align with Version 3.2 and to match the Sponsor's protocol template (Section 7 and Appendix F)
- Added appendix describing Cairo-Bishop grading of tumor lysis syndrome (Section 7.8, Appendix G), and added rasburicase or equivalent as potential prophylaxis for TLS (Section 7.8)
- Clarified circumstances under which positron emission tomography (PET) scan may be performed longer than 30 days prior to screening (Section 8.2.1, Appendix A Schedules of Evaluations)
- Added assessment of International Prognostic Indicator at screening (Section 8.2.1, Appendix A Schedules of Evaluations)
- Prior to LDC, clarified that subjects should not experience a significant worsening in clinical status compared to the initial eligibility criteria that would, in the opinion of the treating physician, increase the risk of adverse events associated with lymphodepleting chemotherapy or exclude them from treatment with JCAR017 (Section 8.2.5.1)
- Clarified that creatinine clearance calculation is required within approximately 48 hours of lymphodepleting chemotherapy to assess the need to adjust the dose of fludarabine (Section 8.2.5.2)
- Added replication-competent lentivirus testing as potential assessment at unscheduled visit (Section 8.2.7)
- Removed the option for repeat leukapheresis for subjects who qualify for retreatment and clarified that retreatment requires additional doses of JCAR017 to be available and remanufacturing is not required (Protocol Synopsis, Section 8.2.8)
- Clarified that the assessments on disease progression/relapse noted in Section 8.2.9 are required when subjects are found to progress at an unscheduled visit.
- Added language clarifying that patients not consenting to the Long-Term Follow-up Study will be followed for survival through public record (Section 8.2.11)
- Added clarification of the Second Primary Malignancies Follow-up Period and language that if a subject develops a second primary malignancy, the Sponsor will request a tumor sample, bone marrow and blood samples (Section 7.12, Section 8.2.12)
- Added new language that that Sponsor will request a sample for viral vector sequence testing if a subject develops second primary malignancy to align with JCAR017 program protocols; clarified language for replication-competent lentivirus testing will be performed on whole blood (Sections 8.3.9.3 and 8.3.9.5)
- Updated Safety reporting requirements to align with program-wide updates (Section 9)
- Updated analysis set names and descriptions (Section 10.2)
- Clarified the definition of a treatment emergent adverse event (TEAE) and adverse events of special interest to ensure alignment across the program (Protocol Synopsis, Section 10.3.6.1)

- Added new language regarding Future Use of Stored Specimens and Data (Section 11.12)
- References were updated (Section 13)
- Removed Karnofsky scale conversion to Eastern Cooperative Oncology Group (ECOG) scale due to inconsistencies in conversion based on various references (Appendix E)
- Updated the JCAR017 Management Guidelines for Cytokine Release Syndrome and Neurologic Toxicities to align with Version 3.2 (Appendix F)
- Updated sponsor name from Juno Therapeutics, Inc. to "the Sponsor" throughout the document
- Corrected misspellings, style, and formatting

JUSTIFICATION FOR AMENDMENT

Significant changes included in this amendment are summarized below:

- **Signature Page**

The Sponsor Signature Page was revised to be consistent with the Celgene protocol template.

- **Investigator Obligations**

The Investigator obligations on the Signature Page were updated to be consistent with European Medicines Agency (EMA) requirements.

Revised section: Signature Page.

- **Study Population**

The exclusion criteria have been modified to exclude subjects with the following:

  - Criterion 14: Tumor invasion of venous or arterial vessels.
  - Criterion 15: Deep venous thrombosis (DVT) or pulmonary embolism (PE) within 3 months of leukapheresis and/or DVT or PE that requires ongoing therapeutic levels of anticoagulation.

These exclusion criteria were added as the result of recommendations from a program-wide Data Safety Monitoring Board after review of an Urgent Safety Measure regarding the death of a subject in study JACR017-BCM-001 (BCM-001), a global Phase 1/2 study of JCAR017 in relapsing/refractory third-line aggressive B-cell lymphoma.

Revised sections: Protocol Synopsis; Section 5.2, Exclusion Criteria.

- **Statistical Methods**

Modified the total sample size to include at least 56 subjects. Indicated that the primary analysis is planned after approximately 80 subjects in total (from Protocol 017006 and/or Study BCM-001, Cohort 2 [TNE Cohort]) have been treated with JCAR017, and these subjects have been followed for at least 6 months or until death, progressive disease, or withdrawal from study. The assumption of the target response rate used to calculate the sample size for this study and associated statistical power was supported by the results of a meta-analysis of available literature across 12 studies of subjects receiving second-line treatment.

Revised sections: Protocol Synopsis; Section 10.5, Sample Size Considerations; Section 10.6.1, Primary Analysis.

- **Safety Monitoring**

The safety monitoring boundaries that will be used to establish a Bayesian framework were modified and will be based on Grade 3 or above JCAR017-related, treatment-emergent neurological toxicity and prolonged Grade 4 and Grade 5 individual safety events and not Grade $\geq$ 3 JCAR017-related adverse events of special interest (AESIs). This change was made so be consistent with Section 10.4 Safety Monitoring Boundaries of the protocol.

The frequency of Data Safety Monitoring Board (DSMB) meetings was changed from quarterly to semiannually over the course of the study to evaluate safety, protocol conduct, and scientific validity and integrity of the trial. This meeting frequency will improve the operational efficiency

of the DSMB as well as to ensure enough new data are available based on the projected rates of subject enrollment across studies. Additional (ad hoc) or more frequent meetings can be convened, if needed, as specified by the DSMB charter.

Revised sections: Protocol Synopsis; Section 4.1, Overall Study Design; Section 4.4.1, Data Safety Monitoring Board; Section 10.4, Safety Monitoring Boundaries.

- **Physical, Routine Neurological, and Mini Mental State Examination (MMSE) Evaluations**

Additional neurological examinations will be performed on Days 1, 8, 15, 22, 29, and 60 to enable the potential early detection of neurologic toxicity. A physical examination inclusive of a neurological examination was also added to the Day 60 evaluation.

Additional Mini Mental State Examinations will be performed on Days 11, 22, and daily until resolution of symptoms in subjects with suspicious and/or diagnosed neurologic toxicity from Day 1 to 29. These additional evaluations have been included to allow for potential calculation of the Car-Related Encephalopathy Score (CRES).

Revised Sections: Section 8.2.5.5, Day 2 Through Day 29; Section 8.2.7, Unscheduled Evaluations; Section 8.3.3, Mini Mental State Examinations; Appendix A, Schedules of Evaluations, Pretreatment, Treatment, and Posttreatment Assessments.

- **Follow-up Visits and Visit Windows**

A 15-month (455 ± 14 days) visit was added for subjects with a first response (CR or PR) documented at the 3-month evaluation after JCAR017 treatment. In addition, the visit windows at 180, 270, and 365 days were modified to occur up to + 35 days after the scheduled evaluation date. This modification will allow for characterizations of the duration of response at 6, 9, and 12 months after first response [redacted].

Revised sections: Section 8.2.6, Follow-up Period: Through Month 24; Appendix A, Schedules of Evaluations, Pretreatment, Treatment, and Posttreatment Assessments.

- **Statistical Analysis**

The Per-protocol Analysis Set was modified to include all subjects who have received at least one infusion of conforming JCAR017 cell product, who meet at least one transplant non-eligible (TNE) criterion and all other eligibility criteria and are compliant with the major requirements of the study protocol. The specific classification of subjects to be included in the Per-protocol Analysis Set will be finalized prior to any formal data analyses or the database lock and this document will be revised accordingly. The Per-protocol Analysis Set will be used in sensitivity analyses of the primary and secondary efficacy endpoints.

The primary efficacy analyses will be based on the total JCAR017-Treated Analysis Set from this study (017006) and/or Study BCM-001 Cohort 2 (TNE Cohort), using Independent Review Committee (IRC) assessments of disease status. The statistical analysis clarified that the primary efficacy analysis will test the null hypothesis of ORR < p0% (this number p0 will be obtained later from a real-world analysis) against the alternative hypothesis that the ORR ≥ p0% at a 1-sided 0.025 level of significance.

A retrospective chart review is being planned to generate a comparable historical control, which will be used to provide a null hypothesis p0 for testing the primary endpoint of objective

response rate (ORR). Table 9 was inserted to show the power to reject the null hypothesis of a response rate less than p0 (a potential estimated range from the retrospective chart review) assuming the target response rate (pa) of 70% using an exact binomial test with 1-sided significance level 0.025 with a sample size of 80 subjects from this study (017006) and/or Study BCM-001 Cohort 2 (TNE Cohort).

Revised sections: Protocol Synopsis; Section 10.2.5, Per-protocol Analysis Set; Section 10.3.2, Primary Endpoint; Section 10.5, Sample Size Considerations.

- **Informed Consent Process**

The informed consent process was modified to clarify the informed consent documentation and filing processes.

Revised section: Section 11.1.4, Subject Informed Consent.

The amendment also includes several other minor clarifications and corrections:

- Added nominal study name to protocol title. Title Page; Protocol Synopsis.
- Changed references to product name from lisocabtagene maraleucel to JCAR017 throughout the protocol except in the protocol title.
- Changed Sponsor contact for safety reporting and updated contact information. Title Page; Section 12.2, Global Drug Safety.
- Clarified tumor histologies potentially appropriate for study inclusion (the actual tumor histologies appropriate for study inclusion remain unchanged). Protocol Synopsis; Section 5.1, Inclusion Criteria.
- Clarified that measurements of diffusing capacity of the lung for carbon monoxide (DLCO) should be adjusted for gender-specific hemoglobin concentration. Protocol Synopsis; Section 5.1, Inclusion Criteria.
- Added history or presence of cerebral edema to list of exclusionary central nervous system (CNS) pathologies. Protocol Synopsis; Section 5.2, Exclusion Criteria.
- Clarified that a baseline tumor biopsy (either a historical sample, or if not available, a fresh tumor sample) will be obtained. Protocol Synopsis; Section 4.1, Overall Study Design.
- Deleted redundant text regarding potential retreatment with JCAR017. Section 6.2.1, Dose Schedule.
- Clarified that suspension of CD4+ cells should be administered immediately after infusion of the CD8+ cells. Section 6.2.2, JCAR017 Preparation, Cell Thawing, and Administration.
- Added that the following additional treatments should be captured on the case report form (CRF) during inpatient and intensive care unit (ICU) stays: Systemic antimicrobial agents (dosage/day), growth factors (dosage/day), systemic anticoagulants (dosage/day), and transfusions (Units transfused/day). Section 6.5.1, Medications Administered During Hospitalizations.

- Clarified that anticancer agents (excluding lymphodepleting chemotherapy and agents administered as an extraordinary measure to treat adverse events (AEs) of uncontrolled JCAR017 proliferation, severe cytokine release syndrome, or neurotoxicity unresponsive to other therapeutic interventions) are prohibited during treatment and follow-up periods unless used as an anticancer agent after lack of adequate response to JCAR017 or progression of lymphoma. Section 6.6, Prohibited Medications.
- Defined the JCAR017-Treated Analysis Set as including all subjects who meet all inclusion/exclusion criteria and have received at least one infusion of conforming JCAR017 cell product. Section 10.2.4, JCAR017-Treated Analysis Set.
- Clarified DOR will be calculated from the first response following JCAR017 treatment. Duration of response (DOR) will be evaluated for subjects who achieve a response and will also be evaluated for subjects whose overall best response is a complete response (CR). Section 3, Study Objectives and Endpoints; Section 10.3.3, Secondary Endpoints.
- Provided justification for the sample size (ie, at least 56 subjects) based on a target response rate of 70% which is supported by the results from a meta-analysis of available literature across 12 studies of subjects receiving second-line treatment. Section 10.5, Sample Size Considerations.
- Revised the cytopenias discussion and added discussion of infections to the list of potential risks associated with treatment with JCAR017. Section 7.3, Cytopenias; Section 7.4, Infections.
- Eliminated human leukocyte antigen (HLA) typing as a protocol-specified evaluation. Appendix A, Schedule of Evaluations and elsewhere, as appropriate.
- Added diffusing capacity of the lung for carbon monoxide (DLCO) as a screening assessment. Section 8.2.1, Screening (Approximately 1-2 Weeks Prior to Leukapheresis); Appendix A, Schedules of Assessment, Screening.
- Indicated the washout period for rituximab is 7 days prior to leukapheresis. Section 8.2.3, Leukapheresis (Approximately 4 Weeks Prior to JCAR017 Administration).
- Appendix A, Schedules of Evaluations, Pretreatment, Treatment, and Posttreatment Assessments, Footnote M was revised to eliminate verbiage relating to positron emission tomography/computed tomography (PET/CT) scans that was not applicable to the patient population included in this study.
- Revised the age groups to be included in comparative analyses to include the following: < 65, ≥ 65 to < 75, ≥ 75 years at the time of the first JCAR017 infusion. Section 10.3.4, Efficacy Subgroup Analysis.
- Clarified that local laboratory reference ranges will be utilized for analyses of clinical laboratory. Section 10.3.6.2, Laboratory Data.
- Added statement that if a subject develops a new malignancy, the Sponsor will request a tumor sample and blood samples. Section 7.12, Replication-Competent Lentivirus, Clonality, and Insertional Oncogenesis.

- Included entire response assessment according to the Lugano Classification based on Cheson, 2014 publication. Appendix B, Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification.
- Updated references with complete publication dates and links to websites, as needed. Section 13, References; Appendix F, Management Guidelines for Cytokine Release Syndrome and Neurologic Toxicities (V3.0), Section 3, References.

1. OVERALL SUMMARY OF CHANGES

Amendment 2 of Protocol 017006 was prepared to incorporate language to emphasize that fludarabine doses should be adjusted in subjects with renal insufficiency. The following major changes were made:

- Added text to emphasize that fludarabine doses should be adjusted in subjects with renal insufficiency. (Adjustment for renal insufficiency is described in the fludarabine label.)
- Updated cytokine release syndrome (CRS) and neurotoxicity (NT) algorithms to version 3.0 (detailed changes presented in Section Section 3)
- Added event-free survival (EFS) as a secondary endpoint
- Specified that the secondary PK assessments will be performed using qPCR, and added an exploratory endpoint for characterization of CAR T cell subpopulations (CD4+ and CD8+) by flow cytometry.
- Specified that cellular immunity may be assessed as an exploratory endpoint.
- Clarified requirement for tumor material in inclusion criterion
- Removed “paresis” as clinically relevant CNS pathology from exclusion criterion
- Removed serum creatinine as an indicator of adequate organ function in inclusion criteria
- Removed erroneous body surface area element of calculated creatinine clearance
- Added information on pseudoprogression
- Added the FACT-Lym subscale to quality of life assessments
- Specified in schedule of events that HRQoL assessments should be performed at disease progression and beyond
- Added more specific information about outpatient treatment
- Removed “pneumocystis pneumonia (PCP) prophylaxis” as a concomitant medication exempt from reporting during hospitalizations
- Clarified that SAEs will be followed until they resolve or return to baseline (previously just return to baseline) and that AE relationship to protocol mandated procedures will no longer be captured on the CRF
- Added information on safety monitoring boundaries
- Clarified translational sampling and assessments to be performed
- Specified that CBCs will be collected unless subjects go on to other anticancer treatment
- Updated background information on CD19 CAR T cells and preliminary data from Study 017001

Other minor clarifications and administrative changes were also made.

1. OVERALL SUMMARY OF CHANGES

Amendment 1 of Protocol 017006 was prepared to incorporate changes [redacted], further clarify various elements of the study, and correct errors identified after finalization.

The following changes were made [redacted]:

- Revised inclusion criterion #5 to enroll subjects who are considered to be transplant ineligible (TNE); to define TNE criteria based on age, performance status and co-morbidities; and to clarify that these subjects must also have adequate organ function (as previously defined in inclusion criterion #9, which has now been deleted and combined with #5).
- Added that a retrospective chart review is being planned to generate a comparable historical control for statistical efficacy evaluation.
- Added criteria for administering lisocabtagene maraleucel.

The following additional changes were also made in this amendment:

- The primary objective was updated to reflect the change in the eligibility criteria regarding TNE subjects.
- The International Nonproprietary Name (INN), lisocabtagene maraleucel, was added.
- Removed 'autologous' from hematopoietic stem cell transplant to align with the change to the eligibility criteria and to update background information.
- Moved language regarding confirmation of diagnosis at relapse from inclusion criterion #7 to inclusion criterion #3 to clarify that histological confirmation of disease should occur at relapse, which is separate from the requirement for enough tumor material for later central confirmation.
- Added to inclusion criterion #8 that subjects who have ECOG performance status of 2 are allowed on study to align with the change to the eligibility criteria regarding TNE subjects.
- Added to exclusion criterion #3 that although previous treatment with CD19-targeted therapy is excluded, prior lisocabtagene maraleucel treatment in this protocol is allowed for the subjects who will be receiving retreatment to clarify that subjects eligible for retreatment will not be excluded because of previous treatment with lisocabtagene maraleucel in this protocol.
- Revised exclusion criterion #5 and added a new exclusion criterion #6 to clarify that subjects who have a history of or active human immunodeficiency virus (HIV) infection at the time of screening are excluded to clarify that not only subjects with active HIV are excluded, but also subjects who have had a history of HIV.
- Added examples of cytotoxic chemotherapeutic agents that are not considered lymphotoxic and an additional example of lymphotoxic chemotherapeutic agents for clarity.

- Removed the anticipated number of study sites at which subjects will be enrolled to allow flexibility in the number of sites at which subjects may be enrolled.
- Added that the estimated total time for all subjects to complete the study is approximately 3 years to allow flexibility in the amount of time it will take for all subjects to complete the study.
- Added that the first treatment response will be done at *approximately* Day 29 to align with the previously defined window for the first response assessment.
- Removed that subjects can receive additional cycles of treatment and removed 'post last dose' throughout the protocol since only one cycle of treatment will be allowed (unless the subject meets the criteria for retreatment as previously defined in the body of the protocol [added to the synopsis for clarity]) to revise the treatment regimen to evaluate one cycle of treatment in this patient population.
- Removed only from the study design description the null hypothesis and the target response rate because a retrospective chart review is being planned to generate a comparable historical control.
- Revised justification for sample size to ensure sufficient sample size for analysis of TNE subjects and to allow analysis of this study independent of BCM-001, if needed.
- Revised the language regarding the studies over which the DSMB has oversight to provide a more detailed description.
- Added the recent FDA approval of Yescarta™, a drug similar to lisocabtagene maraleucel, to the background information for this study to update the background information.
- Clarified that the meta-analysis performed was used to provide a basis for the sizing of this study.
- Revised the purpose of this study to evaluate the use of JCAR017 lisocabtagene maraleucel in subjects who have failed 1 previous line of therapy for aggressive B-cell NHL and are not eligible for HSCT to align with the change to the eligibility criteria regarding TNE subjects.
- Added a new endpoint, duration of CR, for the secondary objective of assessing the rate of CR and durability of antitumor activity to analyze duration of CR in this patient population.
- Language regarding subject discontinuation from further study treatment was revised to clarify that discontinuation from study treatment refers to situations in which a subject does not receive the full dose of JCAR017 and that progressive disease is not a reason for discontinuation of JCAR017 treatment.
- Removed the plan name, Juno's Protocol Product Deviation Plan (PPDP), while the description of the process is still maintained to allow patients to receive lisocabtagene maraleucel even if certain product specifications are not met [redacted].
- Guidelines for the management of CRS and neurotoxicity were updated to align management guidelines across all ongoing lisocabtagene maraleucel protocols.

- Revised the example of high-dose steroids that could be used to manage uncontrolled T cell proliferation for correction.
- For clarity, revised language that Investigators *must* rather than *should* contact the Sponsor immediately if an unexpected pattern of lisocabtagene maraleucel expansion and/or a new malignancy arises.
- Added that PET/CT scans will need to be repeated following the administration of optional bridging chemotherapy to obtain appropriate disease measurements prior to study treatment.
- For correction, removed having no intervening anticancer treatment as a parameter of adequate tissue being available from a previous archived tumor biopsy that was performed since the last relapse or since determination of refractory disease.
- For patient safety, added that subjects who have high baseline tumor burden (as measured by the sum of product of the perpendicular diameters [SPD]) or high serum lactate dehydrogenase (LDH; ≥ 500 U/L prior to the start of lymphodepletion) have a higher risk for developing neurotoxicity and should be closely monitored.
- Removed that archived samples will be destroyed as outlined in the LTFU protocol because this is not applicable to this protocol.
- Clarified that exacerbation of rheumatologic or other autoimmune disorder should be considered in serious adverse event (SAE) reporting.
- The causal relationship with protocol-mandated procedures was removed from the list of items to be evaluated for each AE. Investigators will record AEs resulting from protocol-mandated procedures per the reporting periods specified in Table 10 of the protocol; therefore, the relationship of these AEs to protocol-mandated procedures will already be defined.
- Revised language regarding reporting disease progression as an SAE to clarify how to report disease progression when it meets any of the seriousness criteria.
- Removed that reporting pregnancies ensure subject safety to clarify that reporting the pregnancies will not ensure subject safety.
- Revised ‘dose’ to ‘infusion’ in the definition of the Lisocabtagene Maraleucel-Treated Analysis Set for clarity.
- Added a new analysis set for lisocabtagene maraleucel-treated TNE subjects to allow analysis in alignment with the newly revised eligibility criteria for TNE subjects.
- Corrected verb tense to align with the fact that there is only one primary endpoint for this study.
- Revised the primary efficacy analysis set to be newly added Lisocabtagene Maraleucel-Treated TNE Analysis Set to allow analysis in alignment with the newly revised eligibility criteria for TNE subjects.

- Removed that PK parameters will be estimated from the individual concentration-time profiles using a noncompartmental analysis approach to clarify that a noncompartmental analysis approach will not be used.
- For correction, revised the definition of a treatment-emergent laboratory abnormality as one that, compared to baseline, worsens by at least one grade within 90 days after the final cycle of investigational product lisocabtagene maraleucel, not after lymphodepleting chemotherapy.
- Added that the primary analysis is planned after at least 56 TNE subjects have received lisocabtagene maraleucel and removed the BCM-001 study to clarify when the primary analysis will be performed based on the revised eligibility criteria and allow analysis of this study independent of BCM-001, if needed.
- Added footnote c to tumor biopsy in the screening assessments to clarify that a tumor biopsy may not be required for eligibility.
- Added the Study ID.
- Updated the statistician name and contact information.

Other minor clarifications and administrative changes were also made.