PHASE 1/2 MULTI-CENTER STUDY TO EVALUATE THE SAFETY AND EFFICACY OF ONCT-808 IN ADULT SUBJECTS WITH RELAPSED OR REFRACTORY AGGRESSIVE B-CELL MALIGNANCIES

Investigational Product:	ONCT-808 (ROR1 Chimeric Antigen Receptor [CAR]-positive viable T cells)
Protocol Number:	ONCT-808-101
IND Number:	28759
Sponsor Name and Address:	Oncternal Therapeutics, Inc 12230 El Camino Real, Suite 230 San Diego, CA 92130
Sponsor Signatory:	Salim Yazji, MD Chief Medical Officer Oncternal Therapeutics, Inc.
Emergency Contact:	Yisrael Katz, MD Medical Monitor +1 858-299-5633 clinical@oncternal.com
Protocol Version, Date:	Version 3, 16 JAN 2024

FOR QUALIFIED PHYSICIANS AND THEIR INSTITUTIONAL REVIEW BOARDS/ETHICS COMMITTEES ONLY

CLINICAL PROTOCOL APPROVAL FORM

Protocol Number	ONCT-808-101
Protocol Title:	Phase 1/2 Multi-Center Study to Evaluate the Safety and Efficacy of ONCT-808 in Adult Subjects with Relapsed or Refractory Aggressive B-Cell Malignancies
Date of Document Approval:	16 JAN 2024
Version Number:	3
Sponsor Signatory:	Salim Yazji, MD Chief Medical Officer Oncternal Therapeutics, Inc.
Signature:	

INVESTIGATOR'S AGREEMENT

I have read the attached protocol entitled, "Phase 1/2 Multi-Center Study to Evaluate the Safety and Efficacy of ONCT-808 in Adult Subjects with Relapsed or Refractory Aggressive B-Cell Malignancies," and agree to abide by all provisions set forth therein. 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/Ethics Committee procedures, instructions from Oncternal representatives, the principles of the Declaration of Helsinki, International Council for Harmonisation Good Clinical Practices Guidelines, and local regulations governing the conduct of clinical studies.

I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

TABLE OF CONTENTS

STATEMENT OF COMPLIANCE....10
1. PROTOCOL SUMMARY....11
1.1. Synopsis....11
1.2. Study Schema....15
1.3. Schedules of Assessments....15
LIST OF ABBREVIATIONS AND DEFINITIONS....18
2. INTRODUCTION....22
2.1. Study Rationale....22
2.2. Background....22
2.2.1. Large B-Cell Lymphoma....22
2.2.2. Mantle Cell Lymphoma....23
2.2.3. Receptor Tyrosine Kinase-Like Orphan Receptor 1....24
2.2.4. Nonclinical Experience....26
2.2.4.1. Nonclinical Experience with Zilovertamab....26
2.2.4.2. Nonclinical Experience with ONCT-808....26
2.2.5. Clinical Experience with ONCT-808....26
2.2.5.1. Clinical Experience with Other ROR1 CAR T Cells....27
2.2.5.2. Clinical Experience with Zilovertamab....27
2.2.5.3. Clinical Experience with Zilovertamab Vedotin....27
2.3. Risk/Benefit Assessment....28
2.3.1. Known or Potential Risks....28
2.3.2. Known or Potential Benefits....29
2.3.3. Assessment of Potential Risks and Benefits....29
3. STUDY OBJECTIVES AND ENDPOINTS....31
3.1. Phase 1....31
3.2. Phase 2....31
4. STUDY DESIGN....33
4.1. Overall Study Design....33
4.1.1. Phase 1 Dose Escalation....33
4.1.2. Phase 2 Dose Expansion....35
4.2. Scientific Rationale for Study Design....35

4.2.1. Rationale for Study Population 35
4.2.2. Rationale/Justification of Dose 35
4.2.3. Rationale for Lymphodepeleting Chemotherapy 36
5. STUDY POPULATION 37
5.1. Subject Inclusion Criteria 37
5.2. Subject Exclusion Criteria 38
6. STUDY INTERVENTIONS 41
6.1. Informed Consent 41
6.2. Leukapheresis Period 41
6.3. Bridging Therapy 41
6.4. Lymphodepleting Chemotherapy 42
6.5. ONCT-808 43
6.5.1. Description of ONCT-808 43
6.5.2. Administration of ONCT-808 43
6.5.3. Handling and Accountability of ONCT-808 43
6.5.4. Dispensing and Administration of ONCT-808 43
6.5.5. Packaging and Labeling of ONCT-808 44
6.5.6. Shipping, Storage, and Stability of ONCT-808 44
6.6. Immediate and Post-Treatment Assessment Period 44
6.7. Intermediate Assessment Period 44
6.8. Long-Term Follow-up 45
6.9. Concomitant Therapy or Procedures 45
6.9.1. Permitted Therapies 45
6.9.2. Management of Common Adverse Events 46
6.9.2.1. Cytokine Release Syndrome 46
6.9.2.2. Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) 46
6.9.2.3. Fever and Neutropenia 46
6.9.2.4. Infection Prophylaxis 46
6.9.2.5. Blood Product Support 46
6.9.2.6. Acute Allergic/Infusion Reaction 47
6.9.2.7. Tumor Lysis Syndrome 47
6.9.2.8. Hypotension and Renal Insufficiency 47

6.9.3. Prohibited Medications 47
7. STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWL 48
7.1. Reasons for Subject Removal from the Study 48
7.1.1. End of Study Definition 48
7.1.2. Study Discontinuation 48
7.1.3. Study Stopping Rules 49
7.1.4. Subject Replacement 49
8. STUDY ASSESSMENTS AND PROCEDURES 50
8.1. Response Assessment 50
8.2. Other Assessments and Procedures 50
8.2.1. Demographic/Medical History 50
8.2.2. Physical Examination 51
8.2.2.1. Vital Signs 51
8.2.2.2. Weight and Height 51
8.2.3. Cardiac Assessments 51
8.2.3.1. Electrocardiogram 51
8.2.3.2. ECHO/MUGA 51
8.2.4. Neurological and ICANS Assessments 51
8.2.5. Replication Competent Lentivirus Monitoring 52
8.2.6. Hematology 52
8.2.7. Serum Chemistry 52
8.2.8. Urinalysis 52
8.2.9. Coagulation 52
8.2.10. Pregnancy Test 53
8.2.11. Serum Virology 53
8.2.12. Cytokines 53
8.2.13. Immunogenicity Assessments 53
8.2.14. ONCT-808 Pharmacokinetic Assessments 53
8.2.15. Immunophenotyping 53
8.2.16. Biomarker Assessments 54
8.2.17. Bone Marrow Biopsy and Aspirate 54
8.2.18. Archival or Fresh Tumor Biopsy 54

8.2.19. Blood for Inflammatory Markers....54
8.3. Adverse Events and Serious Adverse Events....54
8.3.1. Definition of an Adverse Event....54
8.3.2. Abnormal Laboratory Values....55
8.3.3. Pre-Existing Medical Conditions....56
8.3.3.1. Hospitalization or Prolonged Hospitalization....56
8.3.3.2. Disease Progression, Relapse, or Disease-Related Death....56
8.3.4. Grading of Adverse Events....56
8.3.5. Relationship to Study Drug....57
8.3.6. Definition of a Serious Adverse Event....59
8.3.7. Definition of Dose-Limiting Toxicity....59
8.3.8. Adverse Events of Special Interest....60
8.3.9. Time Period and Frequency for Collecting AE and SAE Information....60
8.3.10. Recording of Adverse Events and Serious Adverse Events....61
8.3.11. Pregnancy and Reporting....61
8.4. Reporting of SAEs, AESIs, and DLTs....62
8.5. Follow-up of AEs and SAEs....63
8.5.1. Regulatory Reporting Requirements for SAEs....63
8.5.2. Reporting Requirements for Pregnancies....63
9. STATISTICS....65
9.1. Sample Size Determination....65
9.2. Populations for Analysis....65
9.3. Statistical Analyses....65
9.3.1. Statistical Hypotheses....65
9.4. Statistical Analysis Methods....66
9.5. Analysis of the Primary Endpoints....66
9.5.1. Analysis of the Anti-Tumor Endpoints....66
9.5.2. Safety Analyses....66
9.6. Pharmacokinetic Analysis....67
9.7. Baseline Descriptive Statistics....67
9.8. Tabulation of Individual Subject Data....67
10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS....68

10.1. Regulatory, Ethical, and Oversight Considerations 68
10.1.1. Institutional Review Board/Ethics Committee Process 68
10.1.1.1. Written Informed Consent 68
10.1.2. Study Discontinuation and Closure 68
10.1.3. Confidentiality and Privacy 69
10.1.4. Safety Oversight 70
10.1.4.1. Safety Review Committee 70
10.1.5. Study Monitoring 70
10.1.6. Quality Assurance and Quality Control 71
10.1.7. Data Handling and Record Keeping 72
10.1.7.1. Data Collection and Management Responsibilities 72
10.1.7.2. Study Records Retention 72
10.1.8. Protocol Deviations 72
10.2. Financial Disclosure 73
10.3. Publication Policy 73
11. REFERENCES 74
APPENDIX 1. LUGANO CLASSIFICATION 80
APPENDIX 2. EASTERN COOPERATIVE ONCOLOGY GROUP PERFORMANCE STATUS 82
APPENDIX 3. AMERICAN SOCIETY FOR TRANSPLANTATION AND CELLULAR THERAPY CONSENSUS GRADING SYSTEM AND TOXICITY MANAGEMENT 83
APPENDIX 4. ASTCT IMMUNE EFFECTOR CELL-ASSOCIATED NEUROTOXICITY SYNDROME GRADING 84

LIST OF TABLES

Table 1: Schedule of Assessment: Screening Through Month 3 16
Table 2: Schedule of Assessment: Intermediate Assessment Period and Long-Term Follow-Up 17
Table 3: CRS and Neurotoxicity with Approved Autologous CD19 CAR T-Cell Therapies in Relapsed/Refractory B-Cell Lymphoma 29
Table 4: Phase 1 Objectives and Endpoints 31
Table 5: Phase 2 Objectives and Endpoints 31
Table 6: Phase 1 Dose Levels 34

Table 7: Grading of Adverse Event Severity Using CTCAE, Version 5.0.....57
Table 8: Relationship of Study Treatment to Adverse Event 58
Table 9: ASTCT Cytokine Release Syndrome Consensus Grading System [a] 83
Table 10: ASTCT Immune Effector Cell-Associated Neurotoxicity Syndrome Grading[a].....84

LIST OF FIGURES

Figure 1: Survival of Patients with Mantle Cell Lymphoma Who Progressed After Brexucabtagene Autoleucel Therapy (n=6).....24
Figure 2: ROR1 Cell Surface Levels on MCL Patient Cells.....25
Figure 3: Expression of the ROR1 Protein in DLBCL Lymphoma Tissues.....25

STATEMENT OF COMPLIANCE

The study will be conducted in accordance with International Council for Harmonisation Good Clinical Practice (ICH GCP), applicable United States (US) Code of Federal Regulations (CFR), and the country-specific Health or Regulatory Authority regulations and guidance. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from Oncternal Therapeutics, Inc. (the Sponsor) and documented approval from the Institutional Review Board (IRB) or Ethics Committee (EC), except where necessary to eliminate an immediate hazard(s) to the study subjects. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training.

The protocol, Informed Consent Form(s) (ICF[s]), recruitment materials, and all subject materials will be submitted to the IRB/EC for review and approval. Approval of both the protocol and the ICF must be obtained before any subject is enrolled. Any amendment to the protocol will require review and approval by the IRB/EC before the changes are implemented to the study. All changes to the ICF will be IRB/EC approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved ICF.

1. PROTOCOL SUMMARY

1.1. Synopsis

Title

Phase 1/2 Multi-Center Study to Evaluate the Safety and Efficacy of ONCT-808 in Adult Subjects with Relapsed or Refractory Aggressive B-Cell Malignancies

Indication

The indication is for the treatment of adult subjects with relapsed or refractory (R/R) B-cell malignancies.

Study Design

Study ONCT-808-101 is a Phase 1/2, single-arm, open-label, multi-center study to evaluate the safety, tolerability, anti-tumor activity, and pharmacokinetics (PK) of ONCT-808 in subjects with aggressive B-cell non-Hodgkin malignancies, including large B-cell lymphoma (LBCL) and mantle cell lymphoma (MCL). The study will be separated into Phase 1 and Phase 2 portions.

In Phase 1, all subjects will be assigned to dose levels using a 3+3 dose escalation design. Dose escalation or de-escalation will occur based on evaluations by the Safety Review Committee (SRC) in consultation with the Investigators. In Phase 1, approximately 3 dose levels will be evaluated in a 3+3 design, resulting in an expected sample size of up to 18 subjects for dose escalation purposes. After safety has been established and dose escalation may occur at a particular dose level, an additional 3 subjects per dose cohort (maximum 9 subjects per dose level) may be enrolled to further investigate the safety and PK. The estimated maximum sample size in Phase 1 is expected to be 27 subjects. Additional subjects may be enrolled to account for dose-limiting toxicity (DLT) unevaluable subjects. Refer to Section 9.2 for the definition of evaluability.

After the safety, PK, pharmacodynamics, and preliminary efficacy of ONCT-808 have been assessed by the SRC to select the recommended Phase 2 dose (RP2D) in Phase 1 and the 2 dose levels to be studied in Phase 2 (which includes the RP2D), Phase 2 will commence to further validate the dose and evaluate the safety and efficacy of ONCT-808.

The Phase 2 Dose Expansion portion of the study will consist of 2 randomized cohorts. Subjects will be assigned randomly to a Phase 2 cohort, stratified by lymphoma subtype (MCL or LBCL) and will be assigned 1 of 2 doses of ONCT-808 that will be based on the SRC's evaluation of safety data and any PK, pharmacodynamics, and efficacy data from each dose cohort in Phase 1. In Phase 2, up to 18 evaluable subjects will be randomized to 1 of 2 dose-level-specific expansion cohorts in a Simon 2-stage design to exclude an objective response rate (ORR; either complete response [CR] or partial response [PR]) <10%. The hypothesized response rate under treatment is ≥40% and will be evaluated using a one-sided type I error rate of 0.025 with 80% power. Each dosing cohort will evaluate the first 7 subjects for efficacy in Stage 1, and a dosing cohort will be terminated if <2 subjects respond. A cohort progressing to Stage 2 will treat an additional 11 subjects for a total of up to 18 subjects. If at least 5 subjects respond out of the total 18, there will be demonstration of efficacy of ONCT-808 within that dosing cohort and the

corresponding null hypothesis will be rejected. Additional subjects may be enrolled to account for unevaluable subjects. The estimated maximum sample size is 24 per cohort.

All subjects will undergo the following:

- **Screening:** Determining eligibility, within 28 days of enrollment.
- **Enrollment/Leukapheresis:** Subjects will undergo an unstimulated leukapheresis to collect leukocytes for the manufacturing of ONCT-808.
- **Bridging therapy:** If indicated in the Investigator's opinion. Restaging will be required. Bridging therapy prior to leukapheresis must be discussed with the Sponsor.
- **Lymphodepletion:** Prior to receipt of ONCT-808, subjects will receive lymphodepleting chemotherapy.
- **Immediate Post-Treatment Period:** ONCT-808 will be infused intravenously (IV) followed by 14 days of intensive clinical and laboratory observation.
- **Post-Treatment Assessment Period:** Subjects will be evaluated for potential toxicities and disease response for a total of 3 months.
- **Intermediate Period:** Subjects will be evaluated every 3 months up to Month 12, and then every 6 months up to Month 24.
- **Long-Term Follow-Up:** Subjects will be monitored for a total of 15 years.

For study requirements assigned to each study period, please refer to Section 6 for details.

Study Objectives

The primary objectives of Phase 1 are to evaluate the safety and tolerability of ONCT-808 and to determine the maximum tolerated dose (MTD) or maximum administered dose (MAD) of ONCT-808. The SRC will evaluate ONCT-808 safety, PK, pharmacodynamics, and preliminary efficacy and select the RP2D and the 2 dose levels (which includes the RP2D) to be studied in Phase 2.

The primary objective of Phase 2 is to evaluate the efficacy of ONCT-808, as measured by ORR, CR rate, and duration of response (DOR), with tumor response measured according to Lugano 2014 (Cheson, 2014). Secondary objectives will include assessing the PK of ONCT-808, as well as to further characterize the safety and tolerability and evaluate the risk/benefit of ONCT-808 at 2 dose levels, in alignment with the United States (US) Food and Drug Administration's (FDA's) Project Optimus.

Study Eligibility

Adult subjects with R/R aggressive B-cell malignancies, including LBCL and MCL, able to undergo ONCT-808 treatment. Please refer to Section 5 for a complete and detailed list of inclusion and exclusion criteria for both phases of the study.

Treatment

Investigational Product:

- ONCT-808 treatment consists of a single infusion of chimeric antigen receptor (CAR)-transduced autologous T cells (CD4+ and CD8+) administered intravenously at the appropriate target dose (see Section 4.1). Refer to Section 6.5.2 for treatment details.

Lymphodepleting Chemotherapy Treatment:

Subjects will receive a lymphodepleting conditioning regimen as outpatients (unless their clinical condition requires inpatient administration) consisting of cyclophosphamide and fludarabine to induce lymphocyte depletion and create an optimal environment for expansion of ONCT-808. Subjects will initiate lymphodepleting chemotherapy with cyclophosphamide 500 mg/m^2 and fludarabine 30 mg/m^2 on 3 days (usually consecutive) beginning 5 to 7 days before the planned administration of ONCT-808. A lower dose regimen may be used at the Investigator's discretion.

Refer to Section 6.4 for lymphodepleting chemotherapy treatment details.

Procedures

At specific timepoints as outlined in the schedules of assessments (Table 1 for Screening through Month 3 and

Table 2 for the Intermediate Assessment Period and Long-Term Follow-Up), subjects will undergo assessments/procedures including: informed consent, medical history and disease assessment (including and Eastern Cooperative Oncology Group performance status), physical examination (including vital signs and weight), cardiac and neurological assessments, blood draws for complete blood count, chemistry panels, coagulation tests, markers of inflammation, cytokines, exploratory biomarkers lymphocyte subsets, ONCT-808 immunogenicity testing, replication competent lentivirus, and ONCT-808 PK assessments. Women of child-bearing potential will undergo a urine or serum pregnancy test. Subjects will also undergo a baseline electrocardiogram, echocardiogram or multi-gated acquisition cardiac scan, positron emission tomography–computed tomography bone marrow aspirate and biopsy (MCL only), and leukapheresis.

Routinely throughout the conduct of the study, subjects will be asked to report concomitant medications and adverse events and will have their disease assessed.

Safety Review Committee

An SRC that is composed of the Phase 1 study Investigators, cross-functional representatives from the Sponsor, and includes at least 1 independent member with clinical and safety expertise who is not directly involved with the study will review safety data and make recommendations. The SRC will review the safety data from each dose cohort in Phase 1 along with the Investigators and will make dosing recommendations prior to proceeding to the next dose level. The SRC will also select the 2 doses, which will include the RP2D, to be used in the Phase 2 expansion based on a combination of safety, PK, pharmacodynamics, and preliminary efficacy data. The RP2D may fall at or below the MTD or MAD. Additional details are provided in Section 10.1.4.1.

Statistical Considerations

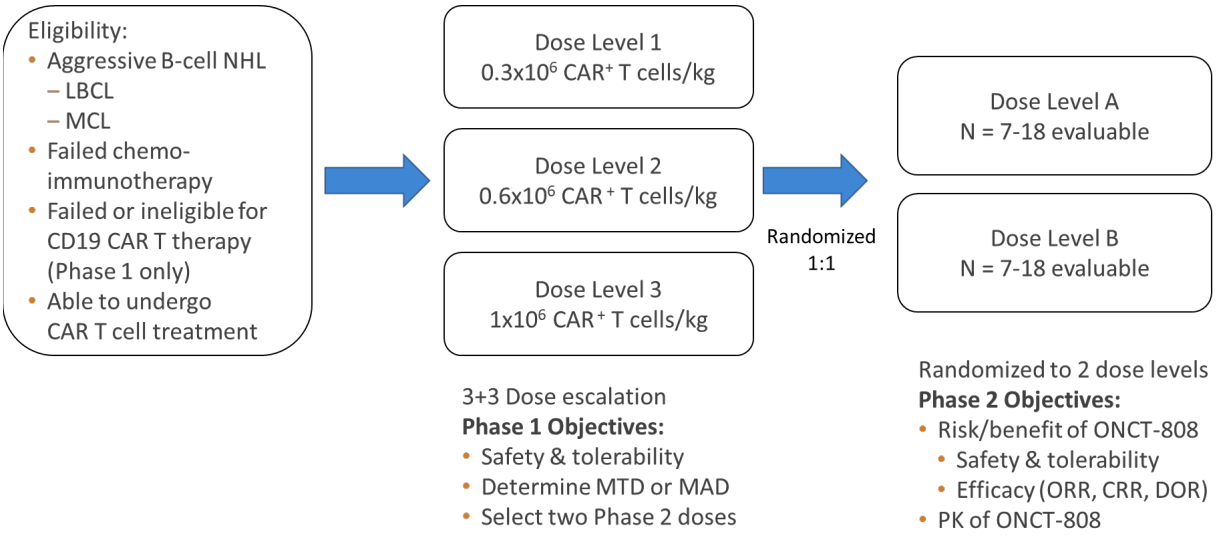
The primary endpoints for the Phase 1 part of the study are the incidence, severity of DLTs, as well as the safety profile of ONCT-808, including incidence, severity, and relationship of

treatment emergent AEs, clinical laboratory assessments, and concomitant medications. Phase 1 Dose Escalation will proceed to determine the MTD and/or RP2D. No hypothesis testing will be performed on Phase 1.

The primary endpoints for the Phase 2 part of the study are ORR, CR rate, and DOR per Lugano 2014 (Cheson, 2014).

Additional details on the statistical analysis methods planned for this study are provided in Section 9.4.

1.2. Study Schema



CAR, chimeric antigen receptor; CRR, complete response rate; DOR, duration of response; LBCL, large B-cell lymphoma; MAD, maximum administered dose; MCL, mantle cell lymphoma; MTD, maximum tolerated dose; NHL, non-Hodgkin's lymphoma; ORR, objective response rate; PK, pharmacokinetic(s)

1.3. Schedules of Assessments

The Schedules of Assessments for Screening through Month 3 and for the Intermediate Assessment Period and Long-Term Follow-Up are provided in Table 1 and Table 2, respectively.

Table 1: Schedule of Assessment: Screening Through Month 3

Procedure		**Screening**	**Leukapheresis Period**	**Lymphodepletion Period[2]**			**Immediate Post-Treatment Period**	**Post-Treatment Assessment Period (From Day 8)**					
Section		5	6.2	6.4			6.5/6.6	6.7					
Day/Month	**Section**	**Within 28 d of enroll**		**LC1**	**LC2**	**LC3**	**D1**	**D1-14 ± 1 d**	**D15 ± 1 d**	**D22 ± 2 d**	**D29 ± 2 d**	**M2 ± 7 d**	**M3 ± 7 d**
Informed consent	6.1	X											
Medical history, ECOG & disease assessment	8.2.1	X											
ECG & LVEF by ECHO or MUGA	8.2.3	X											
Pregnancy test	8.2.10	X		X									X
Blood for HIV, HBV, HCV testing	8.2.11	X											
Blood for inflammatory markers	8.2.19	X											
Urine for urinalysis	8.2.8	X		X									
Blood for hematology	8.2.6	X	X	X			X	D3, 8 & 12	X	X	X	X	X
Blood for chemistry panel	8.2.7	X		X			X	QOD	X		X	X	X
Blood for coagulation tests	8.2.9			X			X	D3	X		X	X	X
PET-CT & disease assessment	8.1	X	X[1]								X		X
Bridging therapy (if indicated)	6.3		X										
Bone marrow biopsy & aspirate	8.2.17		X[3]										
Archival tissue/fresh tumor biopsy	8.2.18		X[4]										
Leukapheresis	6.2		X										
Cyclophosphamide/Fludarabine	6.4			X	X	X							
ONCT-808 infusion IV	6.5.2						X						
Vital signs & physical exam	8.2.2	X	X (+weight)	X			X (+ weight)	QOD[5]	X	X	X	X	X
ICANS monitoring	8.2.4	X					X	QOD	X	X	X	X	X
CRS monitoring	6.9.2.1						X	QOD	X	X	X		
Serum for cytokines	8.2.12	X					X[6]	QOD	X	X	X	X	X
Blood for ROR1 CAR-T PK	8.2.14						X[6]	D3, 8 & 12	X	X	X	X	X
Blood for immunophenotyping	8.2.15						X[6]		X		X		X
Blood/serum for immunogenicity	8.2.13						X[6]		X		X		X
Blood for exploratory biomarkers	8.2.16						X[6]		X		X		X
Serum for RCL analysis	8.2.5		X										X
AEs/Concomitant medication	8.3/6.9	X	X	X	X	X	X	X	X	X	X	X	X

1- Repeat PET-CT only if clinically indicated (e.g., symptomatic deterioration) or if bridging therapy was administered.
2- LC1 is the first day of the 3 days of lymphodepleting chemotherapy, administered outpatient, starting 5 to 7 days prior to ONCT-808 infusion.
3- Bone marrow biopsy and aspirate required prior to lymphodepletion and to confirm CR for subjects with MCL only.
4- Tumor biopsy prior to lymphodepletion only required if archival tissue is not available.
5- Physical exams and assessments performed in the inpatient setting may be performed by any qualified individual operating within the scope of their license.
6- Baseline samples to be collected on the day of ONCT-808 administration prior to the infusion.

Table 2: Schedule of Assessment: Intermediate Assessment Period and Long-Term Follow-Up

		Intermediate Assessment Period					LTFU
Section		6.7					6.8
Procedure **Day**	**Section**	**M6 ± 14 d**	**M9 ± 14 d**	**M12 ± 14 d**	**M18 ± 14 d**	**M24 ± 14 d**	**Annually for a Total of 15 years**
Physical exam[2]	8.2.2	X	X	X	X	X	
PET-CT & disease assessment[1]	8.1	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]
AE/SAEs[2]	8.3	X	X	X	X	X	X
Concomitant medications[2]	6.9	X	X	X	X	X	
Blood for CBC w/differential[2]	8.2.6	X	X	X	X	X	
Blood for ROR1 CAR-T PK[2]	8.2.14	X	X	X		X	
Blood/Serum for immunogenicity[2]	8.2.13			X		X	
Blood for exploratory biomarkers	8.2.16	X		X			
Survival status	6.8						X
Blood for RCL analysis[3]	8.2.5	X		X	X[3]	X[3]	

1- Until progressive disease or initiation of alternate systemic therapy for their cancer. If the subject is still on study after month 24, disease assessments will continue to be performed according to standard of care.
2- Assessments to be performed up to Month 24, or until progressive disease or initiation of alternate systemic therapy; only AEs attributable to ONCT-808 thereafter.
3- If no evidence of RCL is observed at the 3-, 6-, and 12-month timepoints, RCL monitoring will not need to be performed for that subject thereafter.

LIST OF ABBREVIATIONS AND DEFINITIONS

Abbreviation	Explanation
ADC	antibody-drug conjugate
AE	adverse event
AESI	adverse event of special interest
ALC	absolute lymphocyte count
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
ASTCT	American Society for Transplantation and Cellular Therapy
BCL	B-cell lymphoma
βHCG	beta human chorionic gonadotropin
BiPAP	bilevel positive airway pressure
BTK	Bruton's tyrosine kinase
CAR	chimeric antigen receptor
CD	cluster of differentiation
CDX	cell line-derived xenografts
CFR	Code of Federal Regulations
CI	confidence interval
CLL	chronic lymphocytic leukemia
CMV	cytomegalovirus
CNS	central nervous system
COVID-19	Coronavirus disease 2019
CPAP	continuous positive airway pressure
CR	complete response
CRS	cytokine release syndrome
CSF	cerebrospinal fluid
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLBCL	diffuse large B-cell lymphoma
DLT	dose-limiting toxicity
DOR	duration of response
EC	Ethics Committee

Abbreviation	Explanation
ECG	Electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data capture
EEG	electrocardiogram
EOT	end of treatment
FDA	Food and Drug Administration
FDG	fluorodeoxyglucose
GCP	Good Clinical Practice
HBc	anti-hepatitis B core
HbsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HSCT	hematopoietic stem cell transplantation
ICANS	immune effector cell-associated neurotoxicity syndrome
ICE	immune Effector Cell-Associated Encephalopathy
ICF	Informed Consent Form
ICH	International Council for Harmonisation
ICP	intracranial pressure
ICU	intensive care unit
IL	interleukin
INR	international normalized ratio
IRB	Institutional Review Board
IV	intravenous(ly)
LBCL	large B-cell lymphoma
LC	lymphodepleting chemotherapy
LDH	lactate dehydrogenase
LTFU	Long-Term Follow-Up
LVEF	left ventricular ejection fraction
mAb	monoclonal antibody

Abbreviation	Explanation
MAD	maximum administered dose
MCL	mantle cell lymphoma
MMAE	monomethyl auristatin E
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
MUGA	multi-gated acquisition scan
NA	not applicable
NAT	nucleic acid test
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NHL	non-Hodgkin's lymphoma
NOS	not otherwise specified
ORR	objective response rate
OS	overall survival
PCR	polymerase chain reaction
PD	progressive disease
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic(s)
PR	partial response
PT	partial thromboplastin time
QOD	every other day
RCL	replication competent lentivirus
RP2D	recommended Phase 2 dose
R/R	relapsed or refractory
ROR1	receptor tyrosine kinase-like orphan receptor 1
SAE	serious adverse event
SAP	Statistical Analysis Plan
scFv	single chain variable fragment
SD	stable disease
SRC	Safety Review Committee
SOP	Standard Operating Procedures
TEAE	treatment-emergent adverse event

Abbreviation	Explanation
TLS	tumor lysis syndrome
ULN	upper limit of normal
US	United States
USPI	United States Prescribing Information

2. INTRODUCTION

2.1. Study Rationale

This is a Phase 1/2, single-arm, open-label, multi-center study to evaluate the safety and tolerability, anti-tumor activity, and pharmacokinetics (PK) of ONCT-808 and to determine the recommended Phase 2 dose (RP2D) of ONCT-808, an autologous receptor tyrosine kinase-like orphan receptor 1 (ROR1) chimeric antigen receptor (CAR) expressing T-cell therapy, in subjects with relapsed or refractory (R/R) aggressive B-cell malignancies, including large B-cell lymphoma (LBCL) or mantle cell lymphoma (MCL). Patients treated with CAR T-cell therapies targeting CD19 have enjoyed dramatic and prolonged clinical responses with substantial but acceptable toxicities. A ROR1 targeting CAR T cells is scientifically supported, because ROR1 expression is associated with a particularly aggressive tumor phenotype and adverse outcomes. Patients with LBCL or MCL who have failed CD19 CAR T-cell therapy have a particularly dismal prognosis, and their tumors are expected to express ROR1.

2.2. Background

2.2.1. Large B-Cell Lymphoma

LBCL is the most common subtype of NHL, constituting 25% to 30% of adult NHLs in Western countries (Swerdlow, 2008; Flowers, 2010). The age-standardized incidence rate ranges from 4 to 7 per 100,000 person-years in Western countries, with a median age at diagnosis in the 70s (Sant, 2010; Morton, 2006).

Although many patients with LBCL are cured or achieve long-term remission after rituximab and anthracycline-containing first-line immunochemotherapy, and patients who have a relapse with chemotherapy-sensitive disease may be treated with high-dose chemotherapy followed by autologous stem cell transplantation (Sehn, 2020), patients who have disease that is resistant to primary or salvage chemoimmunotherapy or who have had a relapse after transplantation have an extremely poor prognosis. In a large, international, retrospective study involving patients with non-Hodgkin's lymphoma (SCHOLAR-1), Investigators found an objective response rate (ORR) of 26%, a complete response (CR) rate of 7%, and a median overall survival (OS) of 6.3 months with existing therapies among patients who had aggressive B-cell lymphoma (BCL) that was resistant to chemotherapy or who had a relapse within 12 months after autologous stem cell transplantation (Crump, 2017).

Recent developments have supported the effectiveness of therapies that utilize T cells in the treatment of R/R aggressive B-cell non-Hodgkin lymphomas (NHLs). These therapies generally utilize ex vivo genetic engineering of autologous or allogeneic T cells to express CARs that target lineage-specific surface proteins such as CD19. CAR T-cell therapy has shown remarkable effectiveness for patients with R/R CD19-expressing B lymphoid malignancies (Liu, 2020). There are now 3 CD19-targeted CAR T-cell therapies that have been approved by the US Food and Drug Administration (FDA) for adult patients with R/R LBCL after 2 or more lines of systemic therapy. Axicabtagene ciloleucel (YESCARTA® US Prescribing Information [USPI]), tisagenlecleucel (KYMRIAH® USPI) and lisocabtagene maraleucel (BREYANZI® USPI) were approved based on observed ORR rates and remissions that are more durable when compared with similar patients treated with immunochemotherapy (Crump 2017).

Despite high response rates and frequent CRs, relapse following CD19 targeted autologous CAR T-cell therapy is still observed. Fewer than 50% of patients with high-grade B-cell lymphomas (BCL), diffuse large B-cell lymphoma (DLBCL) not otherwise specified (NOS), or LBCL transformed from indolent NHL other than follicular lymphoma were relapse-free by 6 months after treatment with lisocabtagene maraleucel (Abramson, 2020). Thus, there is unmet need for additional therapies for R/R LBCL, including those who have relapsed following CD19 CAR T-cell therapy.

2.2.2. Mantle Cell Lymphoma

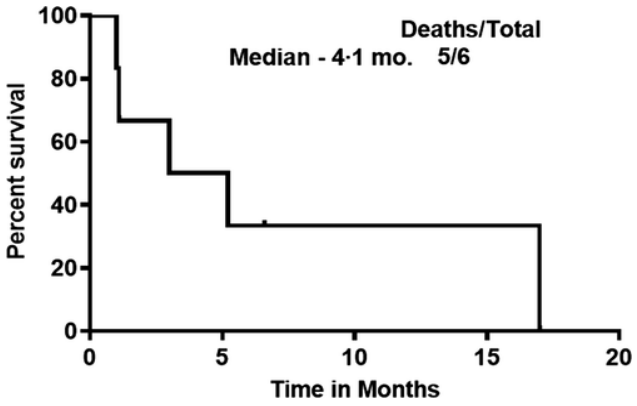
MCL is another form of B-cell NHL with an aggressive clinical course. MCL consists of approximately 7% of the adult NHLs in the US and Europe, with an incidence of approximately 4 to 8 cases per million persons per year. Incidence is shown to increase with age and appears to be increasing overall in the US.

While there are several therapeutic options available to treat patients with R/R MCL, none of these options offer optimal long-term benefit, with most patients relapsing in less than 20 months. Bruton's tyrosine kinase (BTK) inhibitors have greatly improved outcomes in the R/R setting but patients who progress on these agents have a poor prognosis, with an ORR of 25% to 42% and median OS of 6 to 10 months with salvage therapies (Wang, 2020).

Brexucabtagene autoleucel (Tecartus PI, 2021), a CD19 CAR T-cell therapy, was approved by the FDA in 2020 for treatment of R/R MCL under accelerated approval demonstrating durable long-term responses and may confer benefit in patients with high risk characteristics. After ~3 years of follow-up, the ORR was 91% (CR of 68%; 95% CI, 55.2-78.5); medians for DOR, PFS and OS were 28.2 months (95% CI, 13.5 to 47.1), 25.8 months (95% CI, 9.6 to 47.6), and 46.6 months (95% CI, 24.9 to NE), respectively (Wang, 2022).

The rationale to include patients with MCL who have relapsed or are refractory to CD19 CAR T-cell therapy is based on the significant percentage of progressive disease (14 of 56; 25%) in patients who initially responded to CD19 CAR T-cell therapy (Jain, 2021). The median response duration on CD19 CAR T-cell therapy was 6 months (range 1.2 to 31.2 months). Overall, 5 patients had died at the time of last follow-up and the median OS from the time of starting CD19 CAR T-cell therapy to their last follow-up was 17 months, while the median OS after progression on CAR T-cell therapy was only 4.1 months with a 1-year survival of 0% (Figure 1; Jain, 2021).

Figure 1: Survival of Patients with Mantle Cell Lymphoma Who Progressed After Brexucabtagene Autoleucel Therapy (n=6)



Source: Jain, 2021

Therefore, a significant unmet medical need exists for patients with R/R MCL that have disease progression after CD19 CAR T-cell treatment.

The overexpression of ROR1 in many MCL cells combined with the crosstalk observed between ROR1 and multiple signaling pathways promoting cancer cell survival, proliferation, and metastasis provide a very strong rationale for targeting ROR1 for MCL therapy (Yu, 2018).

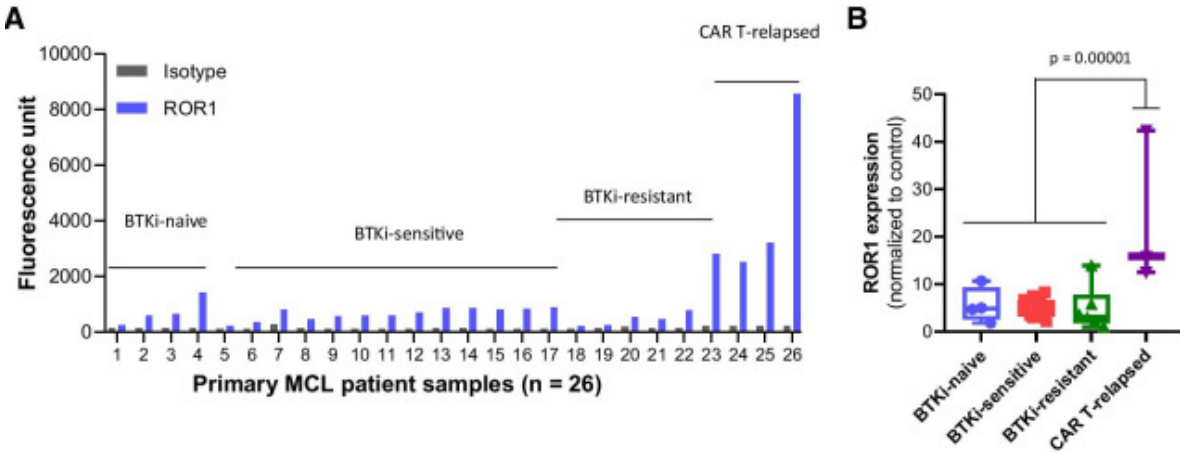
2.2.3. Receptor Tyrosine Kinase-Like Orphan Receptor 1

ROR1 is a type 1 transmembrane protein that shares homology to other receptor tyrosine kinases and shows very high evolutionary conservation (Masiakowski, 1992; Forrester, 1999; Yoda, 2003; Katoh, 2005). It has no known physiological role in the adult but is essential for normal embryogenesis (Oishi, 1999; Al-Shawi, 2001; Matsuda, 2001; Lyashenko, 2010). Expression of the ROR1 gene is suppressed prior to birth (Masiakowski, 1992; Al-Shawi, 2001; Paganoni, 2010).

ROR1 is frequently re-expressed by cancers and its expression is associated with an aggressive phenotype, including invasiveness, metastasis, and resistance to therapy in both hematological and solid tumors (Li, 2010; Zhang, 2012; Daneshmanesh, 2013; Gentile, 2011; Yamaguchi, 2012; O'Connell, 2013; Ida, 2016; Janovska, 2016; Karvonen, 2018). Elevated levels of ROR1 expression in patients' tumors and cell lines is associated with genes involved in epithelial-mesenchymal transition (Cui 2013). High levels of ROR1 expression are associated with shorter treatment-free survival and OS in patients with both hematological and solid tumors (Cui, 2016; Chien, 2016; Zhang, 2014).

High levels of ROR1 protein expression have been found in multiple cancers, including both hematological malignancies such as MCL (Figure 2), chronic lymphocytic leukemia (CLL), acute lymphocytic leukemia, and LBCL (Figure 3) (Yu, 2018; Karvonen, 2018; Daneshmanesh, 2008; Baskar, 2008; Hudecek, 2010; Barna, 2011; Uhrmacher, 2011; Daneshmanesh, 2013; Kotašková, 2016), and in solid tumors including but not limited to breast, lung, colon, head and neck, prostate and pancreatic cancers (Zhang, 2012; Liu, 2015).

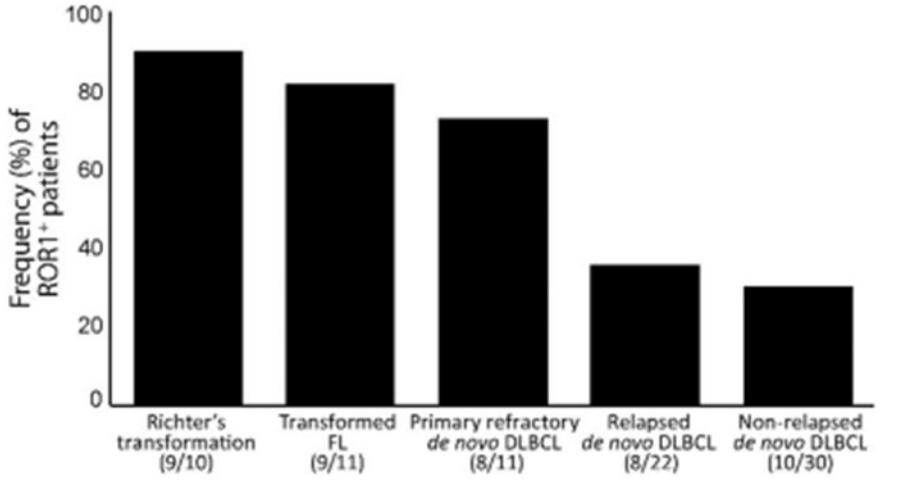
Figure 2: ROR1 Cell Surface Levels on MCL Patient Cells



ROR1 expression on primary MCL patient samples, including CD19 CAR T-cell resistant MCL patient cells. (a) ROR1 expression detected by flow cytometry in primary MCL patient samples (*n*=26), classified into 4 groups: BTKi-naïve (*n*=4), BTKi-sensitive (*n*=13), BTKi-resistant (*n* = 6) and CAR T cell relapsed (*n*=3). (b) Cell surface ROR1 expression of the 4 groups in (a) normalized to controls.
Source: Jiang, 2021

ROR1 expression was observed frequently in primary refractory diffuse LBCL (DLBCL; 7/11, 83%), Richter´s syndrome (9/10, 90%), and transformed follicular lymphoma (9/11, 82%), and also in relapsed (8/22, 36%) and non-relapsed DLBCL patients (10/30, 33%) ($p < 0.001$) (Figure 3; Ghaderi, 2020). A negative survival effect of ROR1 expression was observed in R/R LBCL patients independent of gender and stage (Ghaderi, 2020).

Figure 3: Expression of the ROR1 Protein in DLBCL Lymphoma Tissues



ROR1 expression in aggressive B-cell samples. Numbers in brackets represent the number of ROR1-positive cases compared to the total number of cases in each group.
Source: (Ghaderi, 2020)

ROR1 expression in LBCL patients correlated with lymph node involvement and clinical stage of disease. OS substantially correlated with ROR1 expression. Reduction of ROR1 expression

using ROR1-targeted shRNAs in LBCL cell lines in vitro significantly reduced cell proliferation and PI3K/AKT signaling and significantly increased apoptosis and caspase-3 activation. In xenograft studies using the same shRNA, tumor growth was substantially slower in the shRNA-treatment groups (Mao, 2019).

2.2.4. Nonclinical Experience

2.2.4.1. Nonclinical Experience with Zilovertamab

ONCT-808 expresses a CAR that utilizes the ROR1 binding scFv derived from zilovertamab (previously designated UC-961 or cirmtuzumab), which was developed in a bedside to bench effort based on the detection of autoantibodies to ROR1 in the sera of patients vaccinated with autologous leukemia cells that were capable of inducing apoptosis of CLL cells (Fukuda, 2008). Monoclonal antibodies to ROR1 were developed and selected based on the ability to inhibit the ROR1 intracellular pathway and decrease the engraftment of ROR1 expressing cell lines (Widhopf, 2014), culminating in the development of zilovertamab as a high-affinity humanized IgG1 binding to a functionally important epitope of human ROR1 (Choi, 2015). A GLP human tissue cross reactivity study showed no binding of zilovertamab to any adult tissues from 3 individuals at concentrations up to 5 times the optimal concentration for binding to tumor tissues (Choi, 2015).

2.2.4.2. Nonclinical Experience with ONCT-808

In recently completed nonclinical studies, ROR1 CAR-positive viable T cells were shown to have selective and significant cytotoxic activity compared with activated T cells against both ROR1 positive MEC1 leukemic cells and ROR1 positive MCF-7 breast cancer cells even at low effector to target ratios.

In in vivo efficacy studies using cell line-derived xenografts (CDXs), treatment of mice with 3×10^6 ROR1 CAR-positive viable T cells reduced the leukemic burden of luciferase-labeled ROR1 positive MEC1 cells to background levels by Day 30, and the animals remained disease free without any overt adverse effects (Prussak, 2020).

In an in vivo CDX model using the ROR1-expressing MCL cell line JeKo-1 performed by collaborators at the Karolinska Institutet in Stockholm, Sweden, treatment of mice with 9×10^6 ROR1 CAR-positive viable T cells (ONCT-808) eradicated the JeKo-1 tumor cells, and the animals remained tumor free to the end of the study. There was a dose response for ONCT-808 observed, with lesser levels of tumor control at doses of 3×10^6 or 1×10^6 CAR-expressing T cells. There was no evidence of tumor control in animals who received 12.5×10^6 viable untransduced activated T cells or who received mock treatment.

In an in vivo CDX model using the ROR1-negative T-cell leukemia cell line Jurkat, there was no evidence of tumor control in mice treated with ONCT-808, indicating ONCT-808 killing is specific for ROR1-positive tumor cells.

2.2.5. Clinical Experience with ONCT-808

At the initial dose of $1x10^6$ ONCT-808 CAR T cells per kg in this study, 2 of the 3 subjects achieved complete metabolic response and the third subject fluorodeoxyglucose (FDG) positron-emission tomography-computed tomography (PET-CT). Common adverse events (AEs) in this

dosing cohort included decreased blood counts, pneumonia, and Grade 1 to 2 cytokine release syndrome (CRS) as of an 04 December 2023 data cutoff.

The first subject treated at the second dose level of $3x10^6$ CAR T cells per kg experienced a Grade 5 (fatal) serious adverse event (SAE) consistent with CRS and immune effector cell-associated neurotoxicity syndrome (ICANS). No evidence of the subject's lymphoma was found histologically, based on the initial autopsy report.

2.2.5.1. Clinical Experience with Other ROR1 CAR T Cells

A Phase 1 study (NCT02706392) in 21 patients with ROR1 expressing triple negative breast cancer and non-small cell lung cancer was conducted at the University of Washington testing autologous CD4+ and CD8+ T cells transfected to express a CAR with a binding domain derived from a rabbit monoclonal antibody (mAb) recognizing ROR1 (Hudecek, 2013). In a preliminary report, no dose-limiting toxicities, severe neurotoxicity, or severe CRS were observed (Specht, 2018). CAR T-cell expansion in the peripheral blood without toxicity to normal tissues was observed, but there was evidence of early exhaustion of the CAR T cells with limited persistence and few infiltrating lymphocytes in a tumor biopsy, and tumor regression was not observed in these patients (Srivastava, 2021).

2.2.5.2. Clinical Experience with Zilovertamab

Based on the selective targeting of ROR1, a review of the clinical safety experience with the zilovertamab mAb may be potentially relevant for the initiation of a first-in-human study with ONCT-808. Various doses of zilovertamab, ranging from 0.015 to 20 mg/kg, were given alone for 4 doses over 2 months in 26 patients with CLL in Study HRPP #140141, 'UC-961 (Cirmtuzumab) in Relapsed or Refractory Chronic Lymphocytic Leukemia' (NCT02222688) and the results were published in Cell Stem Cell (Choi, 2018). Zilovertamab was well tolerated up to 20 mg/kg with no DLT or maximum tolerated dose (MTD) identified. There were no characteristic treatment-emergent adverse events (TEAEs) attributed to zilovertamab. Among 22 evaluable patients, no responses (CR or partial response [PR]) were observed with 7 and 5 patients having SD and PD, respectively. However, despite the short duration of treatment, a dose response trend in absolute lymphocyte count reduction was observed and 1 patient had significant reduction of CLL cell infiltration of the bone marrow after therapy. Zilovertamab has also been studied alone and in combination with ibrutinib in Study CIRM-0001, 'A Study of Cirmtuzumab and Ibrutinib in Patients With B-Cell Lymphoid Malignancies' (NCT03088878). Zilovertamab was administered as a single agent at dose levels of 2 to 16 mg/kg and 300 mg and 600 mg fixed doses on Day 1 and Day 14, with observation through Day 28. Zilovertamab was well tolerated in both 33 patients with MCL and 52 patients with CLL, with no DLT and no MTD determined, and there were no characteristic TEAEs attributed to zilovertamab. Starting on Day 28, zilovertamab was administered with daily ibrutinib. No DLTs or Grade 3 AEs occurred that were possibly related to zilovertamab alone. Overall, the safety profile of zilovertamab given with ibrutinib was consistent with that reported for ibrutinib alone, with no increase in the frequency or severity of known ibrutinib-associated AEs, and few if any new AEs.

2.2.5.3. Clinical Experience with Zilovertamab Vedotin

Clinical results from a Phase 1 study of zilovertamab vedotin (MK-2140), an antibody-drug conjugate (ADC) comprising zilovertamab, a proteolytically cleavable linker, and the

antimicrotubular cytotoxic agent monomethyl auristatin E (MMAE) may also be relevant. For the recommended dosing regimen of 2.5 mg/kg every 3 weeks, the ORR was 60% (1 PR, 2 CR) and 47% (4 PR, 3 CR) in heavily pretreated patients with DLBCL (n=5) and MCL (n=15), respectively (Wang, 2022). Importantly, observed toxicities were typical of MMAE-containing ADCs (myelosuppression and neurotoxicity), with no apparent off-tumor, on-target ROR1 mediated organ toxicities.

2.3. Risk/Benefit Assessment

2.3.1. Known or Potential Risks

CAR T-cell therapy is associated with known toxicities, which can be serious or even fatal. CRS, one of the most frequently observed toxicities, can range in severity from low-grade constitutional symptoms to a high-grade syndrome associated with life-threatening hemodynamic instability and multiorgan dysfunction. ICANS is a clinical and neuropsychiatric syndrome that may occur concomitantly with CRS, following resolution of CRS, or in the absence of CRS.

Common AEs in the 3 subjects dosed with $1x10^6$ ONCT-808 CAR T cells per kg in this study included decreased blood cell counts, pneumonia, and Grade 1 to 2 CRS as of an 04 December 2023 data cutoff.

The first subject treated at the second dose level of $3x10^6$ CAR T cells per kg experienced a Grade 5 (fatal) SAE consistent with CRS and ICANS (Section 2.2.5). The SRC recommended testing reduced doses of ONCT-808, $0.3x10^6$ CAR T cells per kg and $0.6x10^6$ CAR T cells per kg, and this protocol was amended (Section 6.5.2).

Rates of CRS and ICANS for 3 approved CD19 CAR T cell products in patients with BCL are provided in Table 3. Note that rates for CRS and ICANS are lower for lisocabtagene maraleucel, which contains the same 4-1BB activating domain as ONCT-808. Intensive monitoring and prompt management of toxicities is essential to minimize the morbidity and mortality associated with these toxicities. Guidance on the assessment, grading and management of these potential risks is described in Appendix 3 and Appendix 4.

Table 3: CRS and Neurotoxicity with Approved Autologous CD19 CAR T-Cell Therapies in Relapsed/Refractory B-Cell Lymphoma

	Tisagenlecleucel[a] N=106		Axicabtagene Ciloleucel[b] N=108		Lisocabtagene Maraleucel[c] N=418	
	All	**Grade 3□**	**All**	**Grade 3□**	**All**	**Grade 3+**
CRS	74%	23%	94%	13%	46%	3.1%
Neurologic Toxicities, including ICANs	58%	18%	57%	29%	33%	10%

CAR, chimeric antigen receptor; CRS, cytokine release syndrome; DLBCL, diffuse large B-cell lymphoma; USPI, United States Prescribing Information.
[a] Kymriah PI, 2022; CRS grading per Penn Grading System.
[b] Yescarta PI, 2022
[c] Breyanzi PI, 2022

There are conflicting data in the literature concerning expression of ROR1 on human tissues, and thus the risk of toxicity to normal tissues from a ROR1 targeting T-cell therapy. Some studies report ROR1 expression in epithelial tissues, including parathyroid, pancreatic islet cells, and the gastrointestinal tract (Hudecek, 2010, Balakrishnan, 2017), while other studies suggest that the ROR1 protein is minimally expressed on normal adult tissues (Fukuda, 2008; Hudecek, 2010; Zhang, 2012; Liu, 2015; Baskar, 2008; Dave, 2012), with the exception of rare B-lymphocyte precursors known as hematogones (Broome, 2011). Results of a nonclinical program investigating ROR1 CAR T cells that utilized a binding domain from a mAb cross-reactive with human and murine ROR1 but otherwise unknown specificity for ROR1 were reported (Rottman, 2017). The ROR1 CAR T cells were shown to accumulate in the lung and cause pulmonary toxicity in a mouse model. The relevance of these results to the potential safety of T cells expressing a CAR with the scFv of zilovertamab, which exhibits high specificity for human ROR1, does not cross-react with murine ROR1, and does not bind to human lung tissue, is unknown.

2.3.2. Known or Potential Benefits

At the initial dose of $1x10^6$ ONCT-808 CAR T cells per kg in this study, 2 of the 3 subjects achieved complete metabolic response and the third subject achieved a PR by FDG PET-CT.

The first subject treated at the second dose level of $3x10^6$ CAR T cells per kg expired 8 days after dosing, but no evidence of the subject's lymphoma was found histologically, based on the initial autopsy report (see Section 2.2.5).

2.3.3. Assessment of Potential Risks and Benefits

As summarized above, administration of ONCT-808 at the initial dose of $1x10^6$ ONCT-808 CAR T cells per kg was associated with tolerable side effects including CRS, and there were early signs of anti-tumor activity. There was one fatal reaction at dose level $3x10^6$ CAR T cells per kg, and no evidence of lymphoma at autopsy.

The SRC reviewed the clinical data and recommended reducing the dose of ONCT-808 to $0.3x10^6$ CAR T cells per kg for the next dosing cohort. The United States (US) Food and Drug

Administration (FDA) also considered this change to be reasonable. The amended dose levels of ONCT-808 are provided in Table 6.

The use of CD19 CAR T-cell therapy in R/R B-cell malignancies is well established for providing high response rates and durable responses, although with known toxicities. ONCT-808 has shown promise in nonclinical efficacy models. The potential risks of common CAR-expressing T-cell therapies such as CRS and ICANS are well known, and safety management protocols have been established. The benefit of evaluating the ROR1 targeting therapy ONCT-808 is unknown, but there is a reasonable chance of observing anti-tumor activity. This study will evaluate and characterize the safety of administering ONCT-808 to subjects with advanced LBCL or MCL, and if warranted will explore its efficacy in the same patient populations.

3. STUDY OBJECTIVES AND ENDPOINTS

3.1. Phase 1

Table 4: Phase 1 Objectives and Endpoints

Primary Objectives	**Primary Endpoints**
• To evaluate the safety and tolerability of ONCT-808. • To determine the MTD or MAD of ONCT-808.	• Incidence, severity, and relationship of DLTs. • Safety profile, including incidence, severity, and relationship of TEAEs, clinical laboratory assessments, and concomitant medications.
• To select a RP2D of ONCT-808, and 2 dose levels (which includes the RP2D) to be tested in Phase 2.	• Evaluation of safety, PK, pharmacodynamics, and preliminary anti-tumor activity by the SRC.
Secondary Objectives	**Secondary Endpoints**
• To evaluate the anti-tumor activity of ONCT-808.	• ORR, CR rate, and DOR according to Lugano 2014 (Cheson, 2014).
• To evaluate the PK of ONCT-808.	• Engraftment, expansion, persistence, and immunophenotype of ROR1 CAR-positive T cells.
Exploratory Objectives	**Exploratory Endpoints**
• Explore the relationship between CAR T cell exposure and responses.	• ONCT-808 PK, anti-tumor activity.
• Explore the relationship between tumor ROR1 expression and anti-tumor activity.	• ROR1 expression, anti-tumor activity.
• Explore the relationship between CAR T cell final product characteristics and CAR T cell PK profiles.	• ONCT-808 release and characterizations results, ONCT-808 PK.

CAR, chimeric antigen receptor; CR, complete response; DLT, dose-limiting toxicity; DOR, duration of response; MAD, maximum administered dose; MTD, maximum tolerated dose; PK, pharmacokinetic; ORR, objective response rate; RP2D, recommended Phase 2 dose; ROR1, receptor tyrosine kinase-like orphan receptor 1; SRS, Safety Review Committee; TEAE, treatment-emergent adverse event

3.2. Phase 2

Table 5: Phase 2 Objectives and Endpoints

Primary Objectives	**Primary Endpoints**
• To evaluate the efficacy of ONCT-808.	• ORR, CR rate, and DOR according to Lugano 2014 (Cheson, 2014).

Secondary Objectives	**Secondary Endpoints**
• To further characterize the safety and tolerability of ONCT-808.	• Safety profile, including incidence, severity, and relationship of TEAEs, clinical laboratory assessments, and concomitant medications.
• To evaluate the risk/benefit of ONCT-808 at 2 dose levels.	• Safety and efficacy profiles.
• To evaluate the PK of ONCT-808.	• Engraftment, expansion, persistence, and immunophenotype of ROR1 CAR-positive T cells.
Exploratory Objectives	**Exploratory Endpoints**
• Explore the relationship between CAR T cell exposure and responses.	• ONCT-808 PK, anti-tumor activity.
• Explore the relationship between tumor ROR1 expression and anti-tumor activity.	• ROR1 expression, anti-tumor activity.
• Explore the relationship between CAR T cell final product characteristics and CAR T cell PK profiles.	• ONCT-808 release and characterizations results, ONCT-808 PK.

CAR, chimeric antigen receptor; CR, complete response; DOR, duration of response; PK, pharmacokinetic; ORR, objective response rate; ROR1, receptor tyrosine kinase-like orphan receptor 1; TEAE, treatment-emergent adverse event

4. STUDY DESIGN

4.1. Overall Study Design

This is a Phase 1/2, single-arm, open-label, multi-center study to evaluate the safety and tolerability, anti-tumor activity, and PK of ONCT-808 in subjects with aggressive B-cell malignancies, including LBCL and MCL. The study will be separated into 2 portions designated as Phase 1 (dose escalation) and Phase 2 (dose expansion). The estimated maximum sample size in Phase 1 is expected to be 27 subjects. In Phase 2, up to 18 evaluable subjects will be enrolled in each indication-specific expansion cohort (an estimated 36 subjects total).

Additional subjects may be enrolled to replace unevaluable subjects, or during dose escalation once a dose level has been cleared. After the safety and tolerability of ONCT-808 have been assessed to select the RP2D in Phase 1, Phase 2 will commence to further validate the dose and evaluate the safety and efficacy of ONCT-808.

All subjects will undergo the following:

- **Screening:** Determining eligibility, within 28 days of enrollment.
- **Enrollment/Leukapheresis:** Subjects will undergo an unstimulated leukapheresis to collect leukocytes for the manufacturing of ONCT-808.
- **Bridging therapy:** If indicated in the Investigator's opinion. Restaging will be required. Bridging therapy prior to leukapheresis must be discussed with the Sponsor.
- **Lymphodepletion:** Prior to receipt of ONCT-808, subjects will receive lymphodepleting chemotherapy.
- **Immediate Post-Treatment Period:** ONCT-808 will be infused intravenously (IV), followed by 14 days of intensive clinical and laboratory observation.
- **Post-Treatment Assessment Period:** Subjects will be evaluated for potential toxicities and disease response for a total of 3 months.
- **Intermediate Period:** Subjects will be evaluated every 3 months up to Month 12, and then every 6 months to Month 24.
- **Long-Term Follow-Up:** Subjects will be monitored for a total of 15 years.

4.1.1. Phase 1 Dose Escalation

The Phase 1 part of the study will enroll subjects with aggressive B-cell NHLs, including LBCL and MCL. In Phase 1, all subjects will be assigned to dose levels using a 3+3 dose-escalation design, using the dose levels shown below (Table 6), with doses calculated based on actual body weight.

Table 6: Phase 1 Dose Levels

Dose Level	Target Dose Viable CAR T Cells/kg	Minimum Dose Viable CAR T Cells	Maximum Dose Viable CAR T Cells
-1	0.15×10^6	7.5×10^6	15×10^6
1	0.3×10^6	15×10^6	30×10^6
2	0.6×10^6	30×10^6	60×10^6
3	1×10^6	50×10^6	100×10^6

CAR, chimeric antigen receptor

Dose escalation or de-escalation will occur based on evaluations by the SRC in consultation with the Investigators, using the following 3+3 dose-escalation rules. Dose-limiting toxicity is defined in Section 8.3.7. The DLT assessment period will be from ONCT-808 administration on Day 1 through Day 29 and be based on DLT evaluable subjects (Section 9.2).

- Subjects will be enrolled in cohorts of 3 subjects per dose level with a minimum interval of 28 days between ONCT-808 dosing for the first 3 subjects in each dose cohort.
- The minimum interval between ONCT-808 dosing for the last subject in 1 cohort and the first subject in a higher dose cohort will be 28 days.
- If no DLT is reported in the initial cohort of 3 subjects, dose escalation can proceed to the next higher dose level.
- If 1 of the first 3 subjects experiences a DLT, the cohort will be expanded to 6 subjects, with a minimum of 28 days between ONCT-808 dosing.
- If 1 of 6 subjects experiences a DLT, dose escalation may proceed to the next higher dose level.
- If 2 or more subjects in a dose cohort experience a DLT, further enrollment in that dose cohort will stop, and dose escalation will stop.
- The dose will be de-escalated to Dose Level -1 if the first 2 subjects treated in Dose Level 1 experience a DLT, or if ≥2 of 6 subjects treated at Dose Level 1 experience a DLT.
- The MTD is the highest dose level in a cohort with no DLT in 3 subjects, or at most 1 DLT in 6 subjects.
- Based on initial safety results of this study (see Section 2.2.5), SRC recommendations, and consultation with the US FDA, the original dose levels -1, 1, 2, and 3 were amended to 0.15×10^6, 0.3×10^6, 0.6×10^6, and 1×10^6 viable CAR T cells/kg respectively, and the 3×10^6 and 10×10^6 viable CAR T cells/kg dose levels were removed. If no MTD is observed up to Dose Level 3, higher dose levels may be evaluated by the SRC if manufacturing yields suggest it is feasible to produce sufficient CAR-expressing T cells. In the absence of establishing the MTD, the highest dose level tested will be considered the maximum administered dose (MAD).

During Phase 1, the SRC and Investigators will meet to review the safety data from each dose cohort and make dosing recommendations prior to proceeding to the next dose level. The SRC may recommend enrolling additional cohorts utilizing doses between, below, or above the doses in Table 6. The SRC will select the RP2D used in the Phase 2 expansion based on a combination of safety, PK, pharmacodynamics, and preliminary efficacy data. The RP2D may fall at or below the MTD or MAD and may be weight-based or a fixed dose (with a 30% reduction for subjects weighing less than 50 kg).

If there is initial evidence of anti-tumor response among subjects treated at more than 1 dose level at or below the MTD or MAD, the SRC may advise that more than 1 dose level be further expanded in Phase 2.

Once a dose level is cleared according to the above per 3+3 dose-escalation rules (i.e., 0/3 DLT or 1/6 DLT), additional subjects who are not DLT evaluable may be enrolled into that dose level, with at least 1 day between dosing each additional subject, to a maximum of 9 subjects per dose level to further evaluate safety. Dose level stopping rules will not apply to these subjects, but the SRC and Investigators will consider their safety experience in making dosing and study conduct decisions.

4.1.2. Phase 2 Dose Expansion

The Phase 2 Dose Expansion portion of the study will consist of 2 randomized cohorts. Subjects will be assigned randomly, stratified by lymphoma subtype (MCL or LBCL), to a Phase 2 cohort and will be assigned 1 of 2 dose levels of ONCT-808 that will be based on the SRC's evaluation of safety data and any PK, pharmacodynamics, and efficacy data from each dose cohort in Phase 1. A planned 18 efficacy-evaluable subjects (Section 9.2) per dose level will be treated at each of the 2 dose levels selected, which will include subjects treated with the RP2D identified during the Phase 1 Dose Escalation part of the study. Phase 2 subjects will not be required to have received prior approved CD19 CAR-T therapy.

Each cohort in Phase 2 will enroll 7 to 18 efficacy-evaluable subjects, following a Simon 2-stage design (see Section 9.5). Unevaluable subjects may be replaced.

4.2. Scientific Rationale for Study Design

4.2.1. Rationale for Study Population

Aggressive NHL, the focus of this study, is generally considered to include AIDS-associated lymphoma, Burkitt lymphoma, primary central nervous system (CNS) lymphoma, LBCL, MCL, peripheral T-cell lymphoma and T-cell lymphoblastic lymphoma (LLS 2022). The T-cell lymphomas and Burkitt lymphoma do not commonly express ROR1, and NHL likely to involve the CNS will not be included for safety reasons, so subjects with LBCL and MCL will be enrolled and treated in this study.

4.2.2. Rationale/Justification of Dose

The appropriate number of ROR1 CAR-expressing T cells required will be calculated based on the subject's weight (kg) and the assigned dose in cells per kg, with minimum and maximum doses indicated in Section 4.1. The initial dose tested was $1x10^6$ viable ROR1 CAR-expressing T cells per kg with a minimum of $50x10^6$ cells and a maximum of $100x10^6$ cells given once by IV

infusion. This initial starting dose was acceptable to the US FDA in a pre-IND interaction, is lower than the top approved dose of most CD19 CAR-expressing T-cell therapies, and is a typical starting dose (Locke 2017; Abramson, 2020).

Based on initial safety results of this study (see Section 2.2.5), Safety Review Committee (SRC) recommendations, and consultation with the US FDA, dose levels -1, 1, 2, and 3 were amended to 0.15×10^6, 0.3×10^6, 0.6×10^6, and 1×10^6 viable CAR T cells/kg, and the 3×10^6 and 10×10^6 viable CAR T cells/kg dose levels were removed.

4.2.3. Rationale for Lymphodepeleting Chemotherapy

The purpose of lymphodepleting chemotherapy prior to the administration of ONCT-808 is to create an immune microenvironment that promotes adoptive transferred T-cell persistence and expansion. This is primarily achieved through promoting homeostatic T-cell proliferation and can lead to activation of certain immune-cell subsets, providing a potential mechanism of improved anti-tumor responses (Bishop, 2022; King, 2004). Lymphodepletion eliminates regulatory T cells and other elements of the immune system that compete for homeostatic cytokines and increases the availability of cytokines such as interleukin (IL)-7 and IL-15 (Klebanoff, 2005). Lymphodepletion with cytarabine and fludarabine has been widely established with CD19 CAR T-cell therapies and has demonstrated improved CAR T cell expansion and persistence, which has led to clinical benefit in patients with R/R NHL (Turtle, 2016). The lymphodepletion regimen (cyclophosphamide 500 mg/m^2 and fludarabine 30 mg/m^2) used in this study is the same as the lymphodepleting chemotherapy regimen used prior to infusion of axicabtagene ciloleucel (Yescarta®) and brexucabtagene autoleucel (Tecartus®).

Given that patients who have failed previous CAR-T therapy may be more extensively pretreated and have lower bone marrow reserve than patients studied in previous CD19 CAR T studies, at the Investigator's discretion a less intensive regimen of lymphodepletion may be used if indicated (Section 6.4).

5. STUDY POPULATION

The Investigator or designee must ensure that only subjects who meet all the following inclusion and none of the exclusion criteria at Screening are offered treatment in the study.

5.1. Subject Inclusion Criteria

1. Subject has histologically confirmed aggressive B-cell NHL, including:
   a. MCL, with diagnosis confirmed by cyclin D1 overexpression or evidence of t(11;14) translocation
   b. LBCL, including:
      – DLBCL NOS
      – Primary mediastinal LBCL
      – High-grade BCL
      – DLBCL arising from indolent lymphoma or CLL
      – Follicular lymphoma grade 3B
      – Richter's syndrome
2. Subject has availability of archival tissue or material from a needle biopsy for immunohistology or is willing to undergo a baseline biopsy if not available.
3. Subject has R/R disease with no available therapy. Specifically, subject must:
   a. Have received prior systemic therapy that has included an alkylating agent and an anti-CD20 mAb, and for LBCL an anthracycline.
   b. Have received and progressed after autologous hematopoietic stem cell transplant (HSCT) or is ineligible for or has refused to receive HSCT.
   c. Have received prior approved CD19 CAR T-cell therapy or is ineligible for or has refused CD19 CAR T for the Phase 1 portion of this study.
4. Subject has had a minimum interval between previous systemic therapy and planned leukapheresis:
   a. Chemotherapy: at least 14 days or 5 half-lives (whichever is shorter)
   b. Focal radiotherapy: at least 7 days
   c. Therapeutic doses of systemic steroids: at least 14 days
   d. Investigational therapy: at least 14 days or 5 half-lives (whichever is shorter)
   e. Biologic therapy, including antibody-drug conjugates or bi-specific immune-cell engaging antibodies: at least 21 days or 5 half-lives (whichever is shorter)
   f. Autologous HSCT: at least 3 months
   g. CD19 targeting CAR-expressing T-cell therapy: at least 6 months.
5. Subject has at least 1 lesion measurable in 2 diameters (nodal lesion >1.5 cm in longest dimension or extranodal lesion >1.0 cm in longest dimension, Cheson, 2014). Lesions that have been previously irradiated will be considered measurable only if progression has been documented following completion of radiation therapy
6. Subject has FDG-avid disease (Deauville score of 4-5).
7. Subject is ≥18 years and ≤75 years of age.

8. Subject has an Eastern Cooperative Oncology Group performance status of 0 or 1.
9. Subject has adequate renal, hepatic, pulmonary, and cardiac function, as determined by meeting the following laboratory parameters:
    a. Absolute lymphocyte count ≥100/uL.
    b. Absolute neutrophil count ≥1,000/uL, or ≥500/uL if due to lymphoma (growth factors allowed).
    c. Hemoglobin ≥8 g/dL (transfusion allowed).
    d. Creatinine clearance ≥50 mL/min.
    e. Platelet count ≥75,000/uL or ≥50,000/uL if due to lymphoma (transfusion allowed).
    f. Serum alanine aminotransferase and aspartate aminotransferase (ALT/AST) ≤2.5 upper limit of normal (ULN).
    g. Total bilirubin ≤1.5 mg/dl, except in subjects with Gilbert's syndrome.
    h. Cardiac ejection fraction ≥50%, by echocardiogram (ECHO) or multi-gated acquisition scan (MUGA).
    i. No clinically significant electrocardiogram findings.
    j. No clinically significant pleural effusion.
    k. Baseline oxygen saturation >92% on room air.
10. Subject has an estimated life expectancy of >12 weeks.
11. Subject has signed the Informed Consent Form before any study procedure is performed.
12. For female subjects of childbearing potential, a negative urine or serum pregnancy test
13. For female subjects of childbearing potential, willingness to use an effective method of contraception from the start of the Screening Phase until ≥3 months after the ONCT-808 infusion. Note: A female subject is considered to be of childbearing potential unless she has had a hysterectomy, bilateral tubal ligation, or bilateral oophorectomy; has medically documented ovarian failure (with serum estradiol and follicle-stimulating hormone levels within the institutional laboratory postmenopausal range); or is menopausal (age ≥50 years with amenorrhea for ≥6 months).
14. For male subjects who can father a child with a female partner of childbearing potential, willingness to use an effective method of contraception and refrain from sperm donation from the start of lymphodepletion until ≥3 months after the ONCT-808 infusion. Note: A male subject is considered able to father a child unless he has had a bilateral vasectomy with documented aspermia or a bilateral orchiectomy.

5.2. Subject Exclusion Criteria

A subject will be excluded from entering the study if any of the following criteria apply:

1. Subject has had prior treatment with any ROR1-targeting therapy.
2. Subject is currently receiving or likely to require systemic immunosuppressive therapy (e.g., prednisone >5 mg daily or equivalent) for any indication from the start of lymphodepleting chemotherapy until Day 28 post ONCT-808 infusion.
3. Subject has known active CNS involvement by malignancy within 6 months.

4. Subject has a history or presence of CNS disorder, such as seizure disorder, cerebrovascular ischemia/hemorrhage, dementia, cerebellar disease, cerebral edema, posterior reversible encephalopathy syndrome, or any autoimmune disease with CNS involvement within 6 months of study entry.
5. Subject has clinically significant (i.e., active) cardiovascular disease: myocardial infarction or coronary artery bypass grafting within 12 months prior to the planned dosing of ONCT-808, unstable angina, congestive heart failure of New York Heart Association Classification Class II or higher (Caraballo, 2019) or serious cardiac arrhythmia requiring medication.
6. If receiving anticoagulation therapy, subject is unable to hold therapy for 3 days prior and 28 days following ONCT-808 administration.
7. Subject has evidence of human immunodeficiency virus infection; or active hepatitis B virus (HBV), or hepatitis C virus (HCV); see Section 8.2.11.
8. Subject has a systemic fungal infection requiring medication in the previous 12 months.
9. Subject has a history of COVID-19 infection with residual lung infiltrate/fibrosis.
10. Subject has a possible requirement for urgent therapy due to ongoing or impending oncologic emergency (e.g., tumor mass effect, tumor lysis syndrome).
11. Subject has a history of severe, immediate hypersensitivity reaction to any of the agents used in this study.
12. Subject has a history of malignancy other than nonmelanomatous skin cancer or carcinoma in situ (e.g., cervix, bladder, breast) that has not been in remission for at least 2 years.
13. Subject has had vaccination with a live, attenuated vaccine ≤6 weeks prior to planned start of the lymphodepleting chemotherapy regimen.
14. Subject who is pregnant or breastfeeding.
15. Subject has any medical condition likely to interfere with assessment of safety or efficacy of study treatment.
16. In the Investigator's judgment, the subject is unlikely to complete all protocol-required study visits or procedures, including follow-up visits, or comply with the study requirements for participation.
17. Subject has a history of autoimmune disease (e.g., Crohn's disease, rheumatoid arthritis, systemic lupus) resulting in end organ injury or requiring systemic immunosuppression/systemic disease modifying agents within the last 2 years.
18. Subject has a history of allogeneic organ transplant.
19. Subject has a history of allogeneic HSCT.
20. Subject has concurrent enrollment in another therapeutic investigational study.
21. Subject has bulky disease (≥ 10 cm for a single lesion or contiguous lesions).
22. Subject has evidence of leukemic transformation.

23. Subject has an active post-CAR T immune-mediated disorder (e.g., Grade ≥2 pneumonitis, thyroiditis).
24. Subject was refractory to prior CAR T therapy, with progressive disease in ≤3 months.

6. STUDY INTERVENTIONS

For the purpose of this study, "study treatment" will refer to lymphodepleting chemotherapy and ONCT-808.

6.1. Informed Consent

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. ICFs will be IRB/EC approved and the subject will be asked to read and review the document. The Investigator will explain the research study to the subject and answer any questions that may arise and will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risk, and benefit of the study. Subjects will have the opportunity to carefully review the written ICFs and ask questions prior to signing. The subjects should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The subject will sign the ICF during the Screening Phase prior to any procedures being done specifically for the study. Subjects must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the signed ICF will be given to the subjects for their records. The informed consent process will be conducted and documented in the source document (including the date), and the ICF signed, before the subject undergoes any study-specific procedures. The rights and welfare of the subjects will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

The subject's signed and dated ICF must be obtained before conducting any study procedures and prior to starting intervention or administering study intervention.

6.2. Leukapheresis Period

Prior to undergoing leukapheresis, subjects will be weighed. Availability of archival tissue for immunohistology will be confirmed, and subjects without archival tissue will undergo a tumor biopsy (see Section 8.2.18). Subjects with MCL will have a bone marrow biopsy and aspirate for disease assessment (see Section 8.2.17).

Leukapheresis product will be collected at a qualified apheresis center following the policy and standard operating procedures (SOPs) of the specific apheresis center. The leukapheresis unit is collected using one of the FDA cleared automated continuous-flow centrifuge type apheresis systems and associated sterile disposable apheresis kits. Immediately following collection, the leukapheresis bag will be packaged per institutional policy and SOPs and be shipped to the manufacturing facility. See the Study Manual for further details.

6.3. Bridging Therapy

If subjects experience progressive disease or require therapy for symptomatic disease after enrollment in the study but prior to their lymphodepleting chemotherapy, the Investigator may administer bridging therapy that is appropriate to the subject's disease and treatment history, in consultation with the Study Medical Monitor.

Bridging therapy, if administered, must be completed at least 5 days prior to initiating lymphodepleting chemotherapy. Bridging therapy prior to leukapheresis must be discussed with the Sponsor.

Further, subjects who receive bridging therapy must undergo another PET-CT scan for restaging and subjects with MCL must have a bone marrow aspirate and biopsy to assess disease status after bridging therapy and prior to receiving lymphodepleting chemotherapy and ONCT-808 (see Section 8.1).

Radiotherapy may be applied for symptom relief, but a measurable lesion must remain unirradiated, and irradiated lesions may not be utilized for disease response assessments.

6.4. Lymphodepleting Chemotherapy

Within 2 days of being treated with lymphodepleting chemotherapy, subjects should have:

- Clinical evaluation to confirm they can safely undergo lymphodepletion and ONCT-808 treatment and to evaluate for any signs of infection. Lymphodepleting chemotherapy should be delayed until resolution of any confounding condition.
- Absolute neutrophil count ≥1,000/uL or ≥500/uL if due to lymphoma (growth factors allowed).
- Creatinine clearance ≥50 mL/min.
- Pregnancy test for female subjects of childbearing potential.
- Confirmation that ONCT-808 is available for administration. If insufficient ONCT-808 product is available for administration for any reason, a repeat manufacturing procedure may be carried out using either cryopreserved leukocytes or freshly collected leukocytes.

Subjects will receive a lymphodepleting conditioning regimen as outpatients (unless their clinical condition requires inpatient administration) consisting of cyclophosphamide and fludarabine to induce lymphocyte depletion and create an optimal environment for expansion of ONCT-808. Subjects will initiate lymphodepleting chemotherapy beginning 5 to 7 days (i.e., Day -7 to Day -5) before the planned administration of ONCT-808. See the prescribing information for fludarabine and cyclophosphamide for information on dose adjustment in renal impairment. Mesna (sodium 2-mercaptoethanesulfonate) may be administered at the Investigator's discretion. Treatment should be administered according to institutional guidelines including hydration; the recommended regimen is:

- Cyclophosphamide 500 mg/m^2 IV over 60 minutes daily for 3 days (usually consecutive) followed each day by:
- Fludarabine 30 mg/m^2 IV over 30 minutes

For subjects with limited bone marrow reserve or chronically low blood counts, a cyclophosphamide dose of 300 mg/m^2 may be used at the Investigators discretion. Assessments should be performed as shown in the Schedule of Assessments (Section 1.3) where LC1 is the first day of lymphodepleting chemotherapy. The 3-day regimen may be started between 5 and 7 days prior to inpatient administration of ONCT-808 and be followed by 2 to 4 days of rest.

No other regimen is allowed for lymphodepletion without consulting the Study Medical Monitor. Delay of ONCT-808 administration for more than 7 days following the end of lymphodepleting chemotherapy must be discussed with the Study Medical Monitor.

6.5. ONCT-808

6.5.1. Description of ONCT-808

ONCT-808 is an autologous T-cell drug product genetically modified by ex vivo transduction with lentivirus vector to express a CAR containing a ROR1-directed single chain variable fragment (scFv) region derived from zilovertamab (previously referred to as cirmtuzumab or UC-961) and including 4-1BB and CD3ζ signaling domains.

Each subject's leukapheresis product will be processed to enrich for T cells, which are then stimulated to expand and transduced with a lentivirus vector to introduce the ROR1 CAR gene. The T cells are then expanded, washed, concentrated, formulated, and cryopreserved to generate the ONCT-808 investigational product under Good Manufacturing Practice and SOPs. Once the product has passed required release tests, it will be transferred or shipped back to the treating facility (see Study Manual).

6.5.2. Administration of ONCT-808

Subjects in both study phases will receive ONCT-808 treatment consisting of a single infusion of CAR-transduced autologous T cells administered intravenously at the appropriate target dose, calculated based on body weight (see Section 4.1). Subjects should be weighed on the day of administration and be pre-medicated with acetaminophen 650 mg PO and diphenhydramine 25 mg IV (or another H1-antihistamine) 30 to 60 minutes prior to infusion of ONCT-808.

Management of cell infusion reactions, e.g., reaction to dimethyl sulfoxide, allergic reaction to the cells, or febrile non-hemolytic infection reactions, should be managed with antihistamines, meperidine, or epinephrine as per institutional standards. Corticosteroids should not be used to manage immediate infusion-related toxicity unless life-threatening and approval of Study Medical Monitor should be sought first, if possible.

If insufficient ONCT-808 product is available for administration for any reason, a repeat manufacturing procedure may be carried out using either cryopreserved leukocytes or freshly collected leukocytes.

6.5.3. Handling and Accountability of ONCT-808

Further information regarding ONCT-808 handling and accountability can be obtained from the Study Manual and ONCT-808 Investigator's Brochure.

6.5.4. Dispensing and Administration of ONCT-808

A pharmacist or other specifically trained and qualified staff member will dispense bags or syringes containing ONCT-808 for infusion (see Study Manual).

6.5.5. Packaging and Labeling of ONCT-808

At completion of ONCT-808 manufacturing, the drug product is filled into sterile cryopreservation bags and frozen in the vapor phase of liquid nitrogen (≤-130°C).

Each bag will be labeled with subject-specific information including subject name, date of birth, donor number, blood type, the manufacturing site, date of manufacture, storage conditions, and volume, and will indicate the product is for autologous use only and investigational use only.

6.5.6. Shipping, Storage, and Stability of ONCT-808

ONCT-808 is transferred from the manufacturing site or shipped in a validated liquid nitrogen dry vapor shipping system by a qualified commercial carrier with real time temperature monitoring.

The ONCT-808 product is stable for up to 3 hours at 2°C to 8°C and at room temperature (20°C to 25°C) in the original cryobag after the cryopreserved cells are thawed. The product is stable for 2 hours once transferred into a secondary bag or syringe, but not more than 3 hours total from the time of thawing.

6.6. Immediate and Post-Treatment Assessment Period

ONCT-808 will be administered in an outpatient setting (unless institutional policies or the subject's clinical condition requires inpatient administration). Subjects who receive ONCT-808 will remain in close proximity to the treating center for at least 28 days following ONCT-808 administration. The initial 7 days of observation may take place either in the outpatient setting or inpatient setting, at the treating Investigator's discretion, with frequent clinical and laboratory assessments to be performed for the first 14 days as shown in the Schedule of Assessments (Table 1). Management of potential or common toxicities including CRS and ICANS is discussed in Section 6.9.2. Hospitalization for treatment related toxicity is at the treating Investigator's discretion and according to institutional guidelines.

Subjects will continue to be evaluated clinically for potential toxicities including DLTs, CRS, and ICANS and to have testing performed weekly up to Day 28 and monthly at Month 2 and Month 3, and more frequently as clinically indicated. Initial disease response to treatment will be evaluated including PET-CT on Day 28 and at Month 3.

Additional evaluations include physical exams and vitals, safety labs, AE/concomitant medications reporting, and peripheral blood collection for PK; other correlative studies will be performed for up to 3 months after ONCT-808 administration as specified in the Schedule of Assessments (Table 1).

6.7. Intermediate Assessment Period

Subjects who receive ONCT-808 will return to be evaluated clinically, to have samples collected, and for disease response and survival status including PET-CT at Months 6, 9, 12, 18, and 24 as shown in the Schedule of Assessments (Table 1). Additional evaluations including physical exams, safety labs, AE/concomitant medications reporting, peripheral blood sample collection for PK, replication competent lentivirus (RCL) analysis, and other correlative studies will be performed for up to 24 months after ONCT-808 administration as specified in the Schedule of Assessments (Table 1).

If the subject experiences disease progression and/or receives other systemic therapy for their malignancy prior to the 24-month period, the Intermediate Assessment Period follow-up will end, and subjects will proceed into Long-Term Follow-up (Section 6.8).

6.8. Long-Term Follow-up

Subjects who receive ONCT-808 will enter Long-Term Follow-up (LTFU) and be contacted by telephone or other electronic means at least annually from Year 3 to Year 15. Yearly review of medical history for RCL-related events should focus on outcomes suggestive of lentiviral disease, such as subsequent cancers, neurologic disorders, and hematologic disorders. Subjects continuing to respond should be followed for disease response assessment according to standard of care. Once a subject experiences disease progression and/or receives other systemic therapy for their malignancy, the details of the regimen should be collected, and subsequent disease assessments will cease, but the subject will remain in LTFU for survival and possibly RCL testing (see Section 8.2.5). Refer to the Schedule of Assessments (Table 2) for assessments required in LTFU. Only those AEs that are considered to be attributable to ONCT-808 should be collected during LTFU. Blood samples may be collected during LTFU for ONCT-808 PK and/or biomarkers.

6.9. Concomitant Therapy or Procedures

Therapy for concomitant medical conditions or for symptom management may be given if clinically indicated at the discretion of the Investigator. Concomitant therapy consists of any medication (e.g., prescription drugs, OTC drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a subject in addition to protocol-mandated treatment from start of leukapheresis until going off study. All such medications should be reported and recorded in the electronic Case Report Form (eCRF). For subjects who have disease relapse/progression or initiate new anti-cancer therapy, only concomitant medications for SAEs possibly or probably related to ONCT-808 per Investigator assessment should be collected. The Investigator's decision to authorize the use of any drug other than study treatments will consider subject safety, the medical need, the potential for drug interactions, the possibility for masking symptoms of a more significant underlying event, and whether use of the drug will compromise the outcome or integrity of the study.

6.9.1. Permitted Therapies

Subjects may receive the following therapies during the study:

- Supportive care including but not limited to antibiotics, analgesics, growth factors, and transfusions.
- Palliative radiation: subjects may receive limited palliative radiation therapy at any time and with schedules at the discretion of the Investigator provided that the schedule does not interfere with protocol-specific assessments. Lesions included in a radiotherapy field may not be used for disease assessments, and appropriate documentation of radiated lesions must be captured in the eCRF.

6.9.2. Management of Common Adverse Events

6.9.2.1. Cytokine Release Syndrome

CRS is a symptom complex attributed with the use of adoptive cell therapies and certain monoclonal antibodies that activate lymphocytes and release cytokines. When cytokines are released, clinical manifestations include cardiac, gastrointestinal, laboratory (coagulation, renal and hepatic), vascular (hypotension), neurological, respiratory, skin, and constitutional (fever, rigors, headaches, malaise, fatigue, arthralgia, nausea, and vomiting). Because the signs and symptoms of CRS are not unique to CRS and may be caused by concomitant conditions and/or underlying disease, other causes of fever, hypotension, and/or hypoxia should be excluded. To characterize its severity, CRS should be graded based on the American Society for Transplantation and Cellular Therapy (ASTCT) CRS consensus grading system (Appendix 4, Table 10; Lee, 2019). In addition to clinical signs and symptoms, if CRS is suspected, cytokines, C-reactive protein, and ferritin levels should be assessed locally and a blood sample collected for central cytokine analysis as per the Schedule of Assessments (Section 1.3).

6.9.2.2. Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)

Neurologic toxicity is an identified safety risk associated with adoptive T-cell based therapies (Lee, 2019). Clinical manifestations include encephalopathy, confusion, delirium, somnolence, aphasia, and seizures (Kymriah PI, 2022; Yescarta PI, 2022). The pathophysiology for neurotoxicity is not fully understood but it is considered to be related to generalized T-cell mediated inflammation rather than direct toxicity of CAR T cells on the brain (Tey, 2014). There are no obvious predictors of neurotoxicity. To characterize the severity, neurotoxicity should be graded using the ASTCT guidelines for grading ICANS (Table 10; Lee, 2019).

6.9.2.3. Fever and Neutropenia

Evaluation for infection source and cases of fever should be treated per standard institutional guidelines. Non-steroidal anti-inflammatory drugs and corticosteroids should be avoided. Subjects who have neutropenic fever should receive broad-spectrum antibiotics. Establishing an even daily fluid balance in subjects who are not hypotensive and not having active tumor lysis syndrome (TLS) is recommended. Use of granulocyte colony stimulating factor is permitted and should be administered according to institutional or published guidelines but should be used with caution for the first 5 days after ONCT-808 infusion or if CRS is suspected.

6.9.2.4. Infection Prophylaxis

Subjects should receive prophylaxis for infection with pneumocystis jiroveci, herpes virus, and fungal infections per National Comprehensive Cancer Network (NCCN) guidelines (NCCN, 2022) or standard institutional practice.

6.9.2.5. Blood Product Support

All blood products should be irradiated and screened for CMV, and subjects should receive platelet and red blood cell transfusions as clinically indicated and according to institutional guidelines.

6.9.2.6. Acute Allergic/Infusion Reaction

Subjects should be closely monitored for occurrence of acute allergic/anaphylactoid infusion reactions such as rigors and chills, rash, urticaria, hypotension, dyspnea, and angioedema during and after ONCT-808 infusion, with management according to standard of care and institutional guidelines. Corticosteroids should be avoided if possible.

6.9.2.7. Tumor Lysis Syndrome

All subjects with significant tumor burden should be considered for prophylaxis of TLS and managed per standard institutional practice.

6.9.2.8. Hypotension and Renal Insufficiency

Hypotension and renal insufficiency should be managed based on the clinical judgment of the Investigator and institutional practice. In general, subjects should be kept well hydrated but closely monitored to prevent fluid overload.

6.9.3. Prohibited Medications

Corticosteroid therapy at doses of >5 mg/day of prednisone or equivalent and other immunosuppressive drugs should be avoided for 7 days prior to leukapheresis and 5 days prior to ONCT-808 administration.

Corticosteroids and other immunosuppressive drugs should be avoided for 3 months after ONCT-808 administration and their use should be discussed with the Study Medical Monitor.

No systemic anti-cancer therapies (including chemotherapy, antibody therapy, immunotherapy, cellular therapy, or other experimental therapies) for the subject's cancer are permitted while the subject is on this study, other than bridging therapy or limited field radiotherapy.

No anticoagulation therapy is allowed for 3 days prior to and 28 days after receiving ONCT-808. Consult the Study Medical Monitor for an urgent requirement for anticoagulation.

Subjects are not allowed to participate concurrently in any other therapeutic clinical or imaging study.

7. STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWL

7.1. Reasons for Subject Removal from the Study

Reasons for subject discontinuation from the study **prior to receiving lymphodepleting chemotherapy and ONCT-808** may include any of the following:

- ONCT-808 product not available.
- Investigator decision, including for progressive disease.
- Noncompliance with study procedures.
- Withdrawal of consent.
- The development of intercurrent illness or other substantial change in the subject's condition or circumstances that would place the subject at unacceptable risk as determined by the Investigator in consultation with the Study Medical Monitor.

Reasons for subject discontinuation from the study **after receiving ONCT-808** may include the following:

- Completion of all protocol-mandated activities.
- Withdrawal of consent.
- Loss to follow-up.
- Study termination by the Sponsor.
- Death.

A discontinuation visit should be conducted that includes the activities indicated for the Day 28 visit. Every effort should be made to obtain a reason for subject discontinuation from the study. The primary reason for study discontinuation should be documented in the eCRF. If a subject withdraws from the study, study staff may obtain survival information from public records.

7.1.1. End of Study Definition

The interim clinical study report will be generated when the last subject has completed their 24 months follow-up visit or has died. LTFU will continue thereafter for a total of 15 years.

7.1.2. Study Discontinuation

The Sponsor may terminate this study at any time; although, LTFU would continue. Investigators will be notified by the Sponsor (or designee) if the study is placed on hold, completed, or closed. Conditions that may lead to study termination may include, but are not limited to:

- Discovery of an unexpected, serious, or unacceptable risk to the subjects in the study, as recommended by the SRC (see Section 7.1.3 on study stopping rules).
- Decision on the part of the Sponsor to suspend or discontinue testing, evaluation, or development of the product.

- Insufficient compliance to protocol requirements.

The Sponsor also has the right to discontinue the study at a site at any time. Reasons for early discontinuation of the study at a specific site may include but are not limited to:

- Excessively slow recruitment.
- Poor protocol adherence.
- Inaccurate or incomplete data recording.
- Noncompliance with ICH guidelines or GCP.

7.1.3. Study Stopping Rules

Any of the following will result in a temporary halt to study enrollment and dosing while the SRC evaluates results and makes recommendations:

- Any Grade 5 AE (except for AEs related to disease progression or clearly unrelated deaths such as a fatal motor vehicle accident).
- Grade 4 (life-threatening) toxicity that is possibly or probably related to ONCT-808 that is unmanageable and unexpected.
- New malignancy (distinct from recurrence/progression of previously treated malignancy) and possibly related to ONCT-808.
- Subject incidence of > 33% for any of the following, regardless of duration (including all subjects from dose escalation and cohort expansion):
    - Grade 3 or higher neurologic events.
    - Grade 4 CRS.
    - Grade 4 vital organ toxicity.
    - Other nonhematologic SAEs.
    - Grade 3 or higher infections (treatment [including lymphodepleting chemotherapy]-related).

Safety data will be reviewed regularly by the SRC. Based on recommendations of the SRC, decisions regarding study conduct including changes to enrollment and remedial actions planned to protect subject safety will be made. In addition, the FDA will be promptly notified if any events trigger a stopping rule and will receive safety reports prepared by the Sponsor with planned remedial actions in response to the triggering event.

7.1.4. Subject Replacement

Subjects who undergo leukapheresis and/or lymphodepleting chemotherapy but who do not receive ONCT-808 for any reason will be replaced. Subjects who are not DLT evaluable as defined in Section 9.2 will be replaced.

Subjects in the dose-escalation cohorts who receive ONCT-808 and who are not DLT evaluable as defined in Section 9.2, or who withdraw prior to Day 28 for reasons other than a protocol-defined DLT (e.g., personal decision, clinical disease progression, or symptomatic deterioration) will be replaced for the purpose of determining whether dose escalation should occur. Subjects who receive ONCT-808 and withdraw prior to Day 28 due to a DLT will not be replaced.

Subjects in the expansion cohorts may be replaced if they are not evaluable for efficacy as defined in Section 9.2 for the purpose of estimating clinical activity of ONCT-808.

Additional subjects may be enrolled beyond the planned sample size to provide enough evaluable subjects for analysis.

8. STUDY ASSESSMENTS AND PROCEDURES

8.1. Response Assessment

Subjects will be evaluated for response by the Investigator based on the Lugano Classification for Malignant Lymphoma (Cheson, 2014; Appendix 1) at the times indicated in the Schedule of Assessments (Section 1.3). Initial disease assessment to confirm subject eligibility can be taken from historical data as long as it was taken within 28 days of enrolling. If bridging therapy is administered, disease assessment must be repeated prior to the start of lymphodepleting chemotherapy.

PET-CT scans of disease-specific sites should be performed as indicated in the Schedule of Assessments (Section 1.3). A separate high-resolution CT scan is not required.

For subjects with MCL, bone marrow biopsy and aspirate are required at baseline (prior to start of lymphodepleting chemotherapy), and is required to confirm a CR.

8.2. Other Assessments and Procedures

Study assessments and procedures should be performed as indicated in the Schedule of Assessments (Section 1.3).

8.2.1. Demographic/Medical History

Demographic data collected should include date of birth, sex at birth, ethnicity, and race.

Medical history represents event(s) starting before informed consent and includes clinically significant diseases, surgeries, non-lymphoma cancer history (including prior cancer therapies and procedures), and reproductive status. Further, use of alcohol or drugs of abuse, and all medications (e.g., prescription drugs, OTC drugs, herbal or homeopathic remedies, nutritional supplements) used by the subject at the time of initial Screening visit will be collected. “Clinically significant” is defined as an event, diagnosis or presence of signs or symptoms, or laboratory value that requires either treatment, medical intervention, and/or additional monitoring or follow-up.

Lymphoma cancer history will include cancer diagnosis, original date of diagnosis, stage at diagnosis, stage at Screening.

Prior cancer treatments (e.g., systemic therapies, surgeries, transplants, and radiation therapy) should be collected and data should include indication, dates of start and end, specific therapy/type, its dose/schedule, route of administration, best response, reason for discontinuation, and if appropriate, site of treatment. If cancer surgery has been performed, information should be collected including the indication, surgery date, surgery intent, and a description of the surgery and outcome.

For concomitant medications at enrollment, the data collection should include the medication being taken, the start dates, dose/frequency, route of administration, and the indication.

Eastern Cooperative Oncology Group performance status (Appendix 2) will be used to evaluate the subject's level of function.

8.2.2. Physical Examination

A complete physical examination will be performed at baseline that includes evaluations of skin, nasal cavities, eyes, ears, lymph nodes, and respiratory, cardiovascular, gastrointestinal, neurological, and musculoskeletal systems.

A targeted physical exam will be performed at each subsequent visit as indicated or as clinically indicated based on symptoms reported.

8.2.2.1. Vital Signs

Vital signs, including sitting blood pressure, pulse rate, body temperature, and respiratory rate, will be performed at each study visit.

8.2.2.2. Weight and Height

Weight (in kilograms) will be obtained as indicated in the Schedule of Assessments (Section 1.3). Height (in centimeters) will be measured only at Screening. Body weight at or near the time of leukapheresis will be used to calculate the dose of ONCT-808 unless there has been a substantial delay or change in weight, in which case body weight near the time of infusion should be used.

8.2.3. Cardiac Assessments

8.2.3.1. Electrocardiogram

12-lead electrocardiograms (ECGs) should be performed, read, and assessed locally. 12-lead ECGs will be obtained with the subject resting in a supine position.

8.2.3.2. ECHO/MUGA

An ECHO or MUGA scan is required to be completed at Screening to evaluate left ventricular ejection fraction (LVEF). Clinically significant cardiac history or symptoms present when the subject signed the informed consent should be reported on the appropriate eCRF page.

Subjects must have an LVEF ≥45% to be included into the study.

8.2.4. Neurological and ICANS Assessments

Subjects with a history of CNS involvement with their lymphoma should have a thorough neurological examination at baseline, and a magnetic resonance imaging (MRI) scan if any abnormalities are noted.

As presented in Section 2.3.1, ICANS is a clinical and neuropsychiatric syndrome that may occur concomitantly with CRS, following resolution of CRS, or in the absence of CRS. Intensive monitoring and prompt management of toxicities is essential to minimize the morbidity and mortality associated with ICANS.

Neurotoxicity will be monitored using ASTCT consensus grading for ICANS based on the Immune Effector Cell-Associated Encephalopathy (ICE) score (Appendix 4, Lee, 2019). ICANS monitoring will occur at the timepoints specified in the Schedule of Assessments (Section 1.3). Unscheduled ICE score assessments should be performed if neurotoxicity is suspected or to document resolution to baseline status or a new baseline in confirmed cases.

8.2.5. Replication Competent Lentivirus Monitoring

Blood will be evaluated for RCL monitoring prior to lymphodepleting chemotherapy and again at approximately 3, 6, 12, 18, and 24 months. If no evidence of RCL is observed at the 3-, 6-, and 12-month timepoints for each subject individually, RCL monitoring will not need to be performed for that subject thereafter.

Yearly review of medical history for RCL-related events should focus on outcomes suggestive of lentiviral disease, such as subsequent cancers, neurologic disorders, and hematologic disorders through Month 24 of this study and will continue in LTFU. A blood sample for RCL testing should be obtained if any potential RCL-related event occurs during intermediate or LTFU.

8.2.6. Hematology

Hematology includes hematocrit, hemoglobin, erythrocyte count, absolute counts of leukocytes (neutrophils, lymphocytes, monocytes, eosinophils, basophils), and platelet count and will be performed at the local laboratory at specified visits per the Schedule of Assessments (Section 1.3), or as clinically indicated.

8.2.7. Serum Chemistry

Clinical chemistry includes sodium, potassium, chloride, bicarbonate, blood urea nitrogen or urea, creatinine, glucose, calcium, phosphorus, magnesium (only at Screening), total protein, albumin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, creatine kinase, lactate dehydrogenase, direct bilirubin, total bilirubin, and uric acid will be performed at the local laboratory at specified visits per the Schedule of Assessments (Section 1.3), or as clinically indicated.

8.2.8. Urinalysis

Urinalysis includes specific gravity, pH, protein, glucose, ketones, bilirubin, urobilinogen, blood, nitrite, leukocyte esterase as assessed by dipstick, and microscopic urinalysis evaluating white blood cells, red blood cells, epithelial cells, bacteria, cast, and crystals will be performed at the local laboratory at specified visits per the Schedule of Assessments (Section 1.3) or as clinically indicated.

8.2.9. Coagulation

Coagulation tests includes assessment of international normalized ratio, prothrombin time, and activated partial thromboplastin time at specified visits will be performed at the local laboratory per the Schedule of Assessments (Section 1.3), or as clinically indicated.

8.2.10. Pregnancy Test

A serum or urine pregnancy test will be performed in female subjects of childbearing potential at specified visits at the local laboratory per the Schedule of Assessments (Section 1.3), or as clinically indicated.

8.2.11. Serum Virology

Virology evaluations are designed to identify subjects with a history of HIV infections, with active HBV or active HCV.

Subjects will be excluded from the study based on the following:

- A history of HIV or positive HIV serology testing unless HIV nucleic acid test (NAT) suggests false positive HIV serology.
- Positive for HBV NAT. Subjects who are HepBSAg+, HepBCore Ab+ but NAT negative on antivirals must be discussed with the Study Medical Monitor.
- Positive NAT for HCV.

8.2.12. Cytokines

Blood for assessment of cytokines will be performed according to local institutional protocols to monitor for CAR T related complications (e.g. interleukin-1 beta (IL-1ß), interleukin-6 (IL-6), interferon-γ, interleukin-8 (IL-8), and tumor necrosis factor alpha (TNF-a) at the timepoints specified in the Schedule of Assessments (Section 1.3). A serum sample will be prepared and shipped for central processing at each timepoint following instructions outlined in the Study Manual.

8.2.13. Immunogenicity Assessments

In the event ONCT-808 may have the potential to induce anti-product antibodies to the CAR protein or other components of the CAR T construct, immunogenicity will be assessed to detect anti-product antibodies or anti-CAR cellular immune responses. Blood for assessment of subject immune response to ONCT-808 will be collected at the timepoints specified in the Schedule of Assessments (Section 1.3). Samples will be prepared and shipped for central processing following instructions outlined in the Study Manual.

8.2.14. ONCT-808 Pharmacokinetic Assessments

Blood for assessment of ROR1 CAR-expressing T cells in peripheral blood will be collected at the timepoints specified in the Schedule of Assessments (Section 1.3). Samples will be prepared and shipped for central processing following instructions outlined in the Study Manual.
A complete blood count panel to determine absolute lymphocyte count (ALC) must be collected on the same day as any PK specimen.

8.2.15. Immunophenotyping

Blood for assessment of peripheral blood lymphocyte subsets by immunophenotype will be collected at the timepoints specified in the Schedule of Assessments (Section 1.3). Samples will

be prepared and shipped for central processing following instructions outlined in the Study Manual.

8.2.16. Biomarker Assessments

Blood for exploratory biomarkers that may be predictive of efficacy or safety will be collected on the indicated days (Section 1.3). Tests may include genetic analyses, gene expression, circulating tumor DNA, or additional cytokines or chemokines as knowledge of CAR T cell biology increases during the study. Samples will be prepared and shipped for central processing following instructions outlined in the Study Manual.

8.2.17. Bone Marrow Biopsy and Aspirate

A bone marrow biopsy and aspirate will be obtained and processed in the local laboratory at baseline for subjects with MCL, unless results are available from testing within the previous 28 days. Testing must be repeated prior to the start of lymphodepletion for subjects with MCL who have bridging therapy and must be repeated for subjects with MCL to confirm CR.
A portion of the marrow aspirate should be prepared and shipped for central processing following instructions outlined in the Study Manual.

8.2.18. Archival or Fresh Tumor Biopsy

An archival tumor sample of either a formalin fixed paraffin embedded tumor block, unstained slides or material from a needle biopsy will be required for eligibility. If an archival sample is not available, subjects must be willing to undergo a fresh tumor biopsy from a safely accessible site to be enrolled onto the study. The fresh tumor biopsy procedure, if required, will be collected during the leukapheresis period and prior to administration of bridging therapy if it is clinically indicated (see the Schedule of Assessments in Section 1.3).

8.2.19. Blood for Inflammatory Markers

Blood for assessment of inflammation (including procalcitonin, C-reactive protein and ferritin) will be collected at baseline. If inflammatory markers or cytokines (see Section 8.2.12) are elevated, or if there is other clinical suspicion of infection, an evaluation for occult infection should be performed.

8.3. Adverse Events and Serious Adverse Events

8.3.1. Definition of an Adverse Event

An AE is any untoward medical occurrence in a patient or clinical study subject temporally associated with the use of study treatment (i.e., lymphodepleting chemotherapy, ONCT-808), whether or not considered related to the study treatment.

NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

DLTs are a subset of AEs that may indicate toxicity that limits further dose escalation. DLTs are defined in Section 8.3.7.

Events Meeting the Definition of Adverse Event

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (i.e., not related to progression of underlying disease). Refer to Section 8.3.10 for recording procedures.
- Exacerbation of a chronic or intermittent pre-existing condition, including either an increase in frequency and/or intensity of the condition. Refer to Section 8.3.10 for recording procedures.
- New conditions detected or diagnosed after study treatment administration even though they may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment(s) or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events NOT Meeting the Definition of Adverse Event (Refer to Section 8.3.10 for recording procedures.)

- The disease/disorder being studied or disease progression as a singular event.
- Any significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the subject's condition.
- A pre-existing disease or condition or laboratory abnormality present or detected before the initial Screening Visit and that does not worsen.
- Laboratory abnormalities not considered clinically significant and not requiring clinical intervention or further investigation. Such abnormalities will be captured as part of laboratory monitoring.
- Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that are not clinically significant.

8.3.2. Abnormal Laboratory Values

Laboratory abnormalities without clinical significance are not recorded as AEs or SAEs. However, laboratory abnormalities (e.g., clinical chemistry, hematology, and urinalysis) that require medical or surgical intervention or lead to study treatment interruption, modification, or discontinuation must be recorded as an AE, as well as an SAE, if applicable. In addition,

laboratory or other abnormal assessments (e.g., ECG, X-rays, vital signs) that are associated with signs and/or symptoms must be recorded as an AE or SAE if they meet the definition of an AE or SAE as described in this section and Section 8.3.1. If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis (e.g., anemia), not the laboratory result (i.e., decreased hemoglobin).

8.3.3. Pre-Existing Medical Conditions

Pre-existing medical conditions that are present before the start of lymphodepleting chemotherapy or following bridging therapy will not be recorded as TEAEs but will be documented as part of the subject's medical history. Pre-existing medical conditions that worsen in frequency, severity, duration, or character after initiation of any study treatment will be recorded as AEs. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the pre-existing medical condition has changed by including applicable descriptors, e.g., "more frequent headaches," "worsening of," or "exacerbation of."

8.3.3.1. Hospitalization or Prolonged Hospitalization

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE (per the definition of SAE in Section 8.3.6), except as specified below.

An event that leads to hospitalization under the following circumstances should not be recorded as an SAE:

- An emergency room or observational unit visit without hospital admission unless other serious criteria are met
- Hospitalization for a procedure scheduled or planned before signing of the ICF
- Admission to the hospital for social or situational reasons (e.g., no place to stay, live too far away to come for hospital visits)

8.3.3.2. Disease Progression, Relapse, or Disease-Related Death

The events of disease progression, relapse, or disease-related death as distinct descriptive terms will not be recorded as AEs but will be assessed as part of the efficacy endpoint of the study and will be recorded in an eCRF separate from the Adverse Event eCRF. New or worsening clinical symptoms and/or laboratory abnormalities attributed to disease progression or relapse will be reported as AEs.

8.3.4. Grading of Adverse Events

The severity of AEs will be graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 5.0 (NCI, 2017). For each AE, the highest severity grade attained should be reported. If a CTCAE criterion does not exist, the Investigator should use the grade or adjectives: Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life-threatening), or Grade 5 (fatal) to describe the maximum intensity of the AE. For purposes of consistency with the CTCAE, these intensity grades are defined in Table 7.

The severity of CRS will also be graded using the ASTCT Cytokine Release Syndrome Consensus Grading System (Appendix 3), and the severity of ICANS will be also graded using

the ASTCT Immune Effector Cell-Associated Neurotoxicity Syndrome Grading system (Appendix 4).

Table 7: Grading of Adverse Event Severity Using CTCAE, Version 5.0

Grade	Adjective	Description
Grade 1	Mild	Sign or symptom is present, but it is easily tolerated, is not expected to have a clinically significant effect on the subject's overall health and well-being, does not interfere with the subject's usual function, and is not likely to require medical attention.
Grade 2	Moderate	Sign or symptom causes interference with usual activity or affects clinical status and may require medical intervention.
Grade 3	Severe	Sign or symptom is incapacitating or significantly affects clinical status and likely requires medical intervention and/or close follow-up.
Grade 4	Life-threatening	Sign or symptom results in a potential threat to life.
Grade 5	Fatal	Sign or symptom results in death.

CTCAE, Common Terminology Criteria for Adverse Events

The distinction between the seriousness and the severity of an AE should be noted. Severe is a measure of intensity; thus, a severe reaction is not necessarily a serious reaction. For example, a headache may be severe in intensity, but would not be classified as serious unless it met one of the criteria for serious events (as listed in Section 8.3.6).

Should a pregnancy occur, it must be reported and recorded on the Sponsor's pregnancy form. Pregnancy in itself is not regarded as an AE unless there is a suspicion that a study treatment may have interfered with the effectiveness of a contraceptive medication.

The outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented even if the subject was discontinued from the study.

All reports of congenital abnormalities/birth defects in a fetus are SAEs. Spontaneous abortion, induced abortion due to complications, stillbirth, and neonatal death criteria should also be reported and handled as SAEs. Elective abortions without complications should not be handled as SAEs but should be reported as the outcome of the pregnancy in the pregnancy form.

8.3.5. Relationship to Study Drug

An Investigator who is qualified in medicine must make the determination of relationship to the study treatment for each AE (unrelated, possibly related, or probably related). The Investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the study treatment using the descriptions provided in Table 8.

Table 8: Relationship of Study Treatment to Adverse Event

Relationship	Description
Definite	A clinical event in which a relationship to the use of the study treatment seems definite because of such factors as consistency with known effects of the drug; a clear temporal association with the use of the drug; lack of alternative explanations for the event; improvement upon withdrawal of the drug (de-challenge); and recurrence upon resumption of the drug (rechallenge).
Probable	A clinical event in which a relationship to the study treatment seems probable because of such factors as consistency with known effects of the drug; a reasonable temporal association with the use of the drug; lack of alternative explanations for the event; and improvement upon withdrawal of the drug (de-challenge).
Possible	A clinical event with a reasonable temporal association with administration of the study treatment, and that is not likely to be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking.
Unlikely	A clinical event with a temporal relationship to study treatment administration that makes a causal relationship improbable and for which other factors suggesting an alternative etiology exist. Such factors might include a known relationship of the clinical event to a concomitant drug, past medical history of a similar event, the subject's disease state, intercurrent illness, or environmental factors.
Unrelated	A clinical event in which a relationship to the study treatment seems improbable because of factors such as inconsistency with known effects of the study drug; lack of a temporal association with study drug administration; lack of association of the event with study drug withdrawal or rechallenge; and/or presence of alternative explanations for the event. Alternative explanations might include a known relationship of the clinical event to a concomitant drug, past medical history of a similar event, the subject's disease state, intercurrent illness, or environmental factors.

If no valid reason exists for suggesting a relationship, then the AE should be classified as "unrelated." If there is any valid reason, even if undetermined, for suspecting a possible cause and-effect relationship between the study drug and the occurrence of the AE, then the AE should be considered "related."

If the relationship between the AE/SAE and the study drug is determined to be "possible" or "probable" the event will be considered to be related to the study treatment for the purposes of expedited regulatory reporting.

8.3.6. Definition of a Serious Adverse Event

SAEs are required to be reported by the Investigator to the Sponsor immediately (i.e., no more than 24 hours after awareness of the event; refer to Section 8.3.10 for recording procedures).

If an event is not an AE per the definition above then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease; see Section 8.3.1).

An SAE is defined as any untoward medical occurrence that, at any dose:

- Results in death
- Is life-threatening
  - The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in a substantial disruption of a person's ability to conduct normal life functions, i.e., the AE resulted in a significant, persistent, or permanent change, impairment, damage or disruption in the subject's body function/structure, physical activities, and/or quality of life.
- Is a congenital anomaly/birth defect.
- Other situations NOS:
  - Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
  - Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias, or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an AE (e.g., rated as mild, moderate, or severe, or according to NCI-CTCAE; see Section 8.3.4); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each AE recorded on the eCRF.

8.3.7. Definition of Dose-Limiting Toxicity

Dose-limiting toxicities are defined as any toxicity defined below occurring within the 28 days after infusion of CAR T cells:

- Death (except due to disease progression).

- Grade 4 CRS of any duration.
- Grade 3 CRS that does not improve to Grade 2 or less in 3 days following adequate therapy.
- Grade 3 or higher ICANS of any duration.
- Grade 3 toxicity involving vital organs (e.g., cardiac, pulmonary), except Grade 3 or 4 renal or liver function tests, that do not improve to Grade 2 or less within 7 days.
- Grade 4 hematologic toxicity that does not improve to Grade 2 or less within 28 days.
- Grade 3 or higher infections, not including febrile neutropenia attributable to myelosuppression from lymphodepleting chemotherapy.

CRS and ICANS will be graded according to the ASTCT system (Lee, 2019); see Appendix 3 and Appendix 4.

During the DLT evaluation period (Day 1 through Day 28) of the dose-escalation cohorts, TEAEs identified as DLTs are required to be reported by the Investigator to the Sponsor immediately (no more than 24 hours after learning of the event), who will notify the SRC. Refer to Section 8.3.10 and Section 8.4 for recording and reporting procedures.

8.3.8. Adverse Events of Special Interest

The adverse events of special interest (AESIs) in this protocol will be:

- CRS.
- ICANS.
- Infusion-related reaction (≥ Grade 3) during or after ONCT-808 administration.
- TLS.
- Secondary malignancies.
- Clinically significant systemic infections.
- Prolonged cytopenias (≥ Grade 3, ≥ 21 days).
- Autoimmune disorders.

AESIs that fulfill criteria of an SAE must be reported by the Investigator to the Sponsor as an SAE immediately, within 24 hours after becoming aware of the event (see Section 8.4).

8.3.9. Time Period and Frequency for Collecting AE and SAE Information

Investigators will seek information on AEs at each subject contact. All AEs will be collected and recorded in the subject's medical record and on the Adverse Event eCRF as follows:

- From signing of ICF until first dose of any study treatment (i.e., lymphodepleting chemotherapy, ONCT-808): Any SAEs or AEs that are due directly to study-related procedures/assessments, and AEs leading to subject/study discontinuation.
- From first dose of any study treatment through Month 24 of the post-treatment follow-up period OR until progressive disease OR until subject/study discontinuation

or initiation of subsequent anti-cancer therapies, whichever occurs first: All AEs and SAEs.

- After Month 24 of the post-treatment period OR after subject/study discontinuation OR after progressive disease, OR after initiation of subsequent anti-cancer therapies: only AEs or SAEs attributed to ONCT-808 treatment.

See Section 8.3.10 for instructions on recording AEs and SAEs, including abnormal laboratory values; pre-existing medical conditions; hospitalization; and disease progression, relapse, or disease-related death.

For each AE recorded on the Adverse Event eCRF, the Investigator will make an assessment of seriousness (Section 8.3.6), severity (Section 8.3.4), and causality (Section 8.3.5).

SAEs are required to be reported by the Investigator to the Sponsor immediately (i.e., no more than 24 hours becoming aware of the event). See Section 8.4 for reporting instructions.

Investigators are not obligated to actively seek AE or SAE collection after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study and he/she considers the event to be reasonably related to the study drug or study participation, the Investigator must promptly notify the Sponsor.

8.3.10. Recording of Adverse Events and Serious Adverse Events

When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.

The Investigator is responsible for ensuring all relevant information is recorded on the Adverse Event eCRF and SAE eCRF, as applicable.

The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE. Avoid the use of vague, ambiguous, or colloquial expressions.

To clearly define the timing of AE onset on the day of the first dose of conditioning and the first administration of ONCT-808, the time of onset of AEs will be recorded.

Refer to Section 8.3.1 and Section 8.3.6 for definitions of AEs and SAEs, respectively.

8.3.11. Pregnancy and Reporting

Each female subject should be instructed to inform the Investigator immediately if she becomes pregnant at any time between the start of study Screening until 30 days after the last administration of study treatment.

The Investigator should counsel the subject regarding the possible effects of study drug exposure on the fetus and the need to inform the study center, the Study Medical Monitor, and the Sponsor (or designee) of the outcome of the pregnancy.

Neither the pregnancy itself nor an induced elective abortion to terminate the pregnancy without medical reasons is considered an AE; such occurrences should be reported on the appropriate

pregnancy report forms. However, if the outcome of the pregnancy meets the criteria for classification as an SAE (i.e., spontaneous abortion, induced abortion due to complications, stillbirth, neonatal death, or congenital anomaly [including that in an aborted fetus]), the Investigator should follow the procedures for reporting SAEs (i.e., report the event to the Sponsor [or designee]) and follow-up by submission of the appropriate AE electronic Case Report Forms (eCRFs; see Section 8.3.10).

Information regarding any pregnancy in a study subject or the female partner of a male subject must be documented on a pregnancy report form and forwarded to the Sponsor (or designee) within 24 hours of becoming aware of the pregnancy. Monitoring of the pregnancy in both female study subjects and female partners of male study subjects should continue until the conclusion of the pregnancy. For female partners of male study subjects, such monitoring applies if they became pregnant in the period from the subject's start of ONCT-808 until 30 days after the subject's last dose of treatment. The outcome of the pregnancy should be reported on the pregnancy outcome report form within 5 days of the conclusion of the pregnancy. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported to the Sponsor (or designee).

8.4. Reporting of SAEs, AESIs, and DLTs

The Investigator or designee will notify the Sponsor or their designee and the IRB, if necessary, immediately and not later than 24 hours after knowledge of the SAE/serious AESI/DLT. The Investigator will submit any updated event data to the Sponsor within 24 hours of it being available.

The following is a list of events that the Investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study drug:

- SAEs, including serious AESIs (defined in Section 8.3.6 and Section 8.3.8).
- DLTs during the DLT assessment window (defined in Section 8.3.7).
- Pregnancies (see Section 8.3.11 for details on reporting requirements).

The investigative site personnel will be responsible for submitting the completed SAE/serious AESI/DLT and pregnancy reports to the Sponsor within 24 hours of discovery or notification of the events. The study site will be instructed to de identify (i.e., black out with permanent marker) associated medical records of confidential information prior to sending to the Sponsor.

The primary mechanism for reporting an SAE to the Sponsor will be through the electronic data capture (EDC) system. The Sponsor safety group will be notified electronically via email. If the study site has a temporary interruption in its internet access or computer access, a paper back-up SAE form will be completed and submitted to the Sponsor safety group. When the EDC system becomes available, the SAE information must be entered within 24 hours.

Collection of SAEs during the course of the study are described in Section 8.3.10. Any SAE ongoing when the subject completes the study or discontinues from the study will be followed by the Investigator until the event has resolved, stabilized, or returned to baseline status.

8.5. Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each subject at subsequent visits/contacts. The Investigator must continue to follow the subject until satisfactory resolution stabilization, subsequent anti-cancer therapy is initiated, the subject is lost to follow-up, or the subject withdraws consent.

Procedures for follow-up of AEs and SAEs is as follows:

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare professionals.
- If a subject dies during participation in the study or during a recognized follow-up period, the Investigator will provide a copy to the Sponsor of any post-mortem findings, including but not limited to histopathology.
- New or updated information will be recorded in the originally completed eCRF.
- The Investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

All pregnancies reported during the study should be followed according to the instructions provided in Section 8.5.2.

8.5.1. Regulatory Reporting Requirements for SAEs

Prompt notification by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities toward the safety of subjects and the safety of a study treatment under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local Regulatory Authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the Regulatory Authority, IRBs/ECs, and Investigators.

Per 21 CFR 312.32, Investigator safety reports must be prepared for suspected unexpected serious adverse reactions, except those related to protocol-mandated procedures according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.

An Investigator who receives an Investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/EC, if appropriate, according to local requirements.

8.5.2. Reporting Requirements for Pregnancies

There are no relevant clinical data with ONCT-808 in pregnant or lactating women, and animal reproductive studies have not been conducted. The effects of ONCT-808 on fertility and the developing fetus are unknown. If the subject or partner of a subject participating in the study becomes pregnant during the study at any time after start of study treatment, the Investigator

should report the pregnancy to the key Sponsor contact, including the Drug Safety Team within 24 hours of receiving notification.

The pregnancy itself is not considered an AE, nor is an induced elective abortion to terminate a pregnancy without medical reasons. If the outcome of the pregnancy was abnormal (e.g., spontaneous abortion), the Investigator should report the abnormal outcome as an AE.

9. STATISTICS

9.1. Sample Size Determination

In Phase 1, approximately 3 dose levels will be evaluated in a 3+3 design, resulting in an expected sample size of up to 18 subjects for dose escalation purposes. After safety has been established and dose escalation may occur at a particular dose level, an additional 3 subjects per dose cohort (maximum 9 subjects per dose level) may be enrolled to further investigate the safety and PK. The estimated maximum sample size in Phase 1 is expected to be 27 subjects. Additional subjects may be enrolled to account for DLT unevaluable subjects (Section 7.1.4).

In Phase 2, up to 18 evaluable subjects will be randomized to 1 of 2 dose level-specific expansion cohorts in a Simon 2-stage design to exclude an ORR <10%. The hypothesized response rate under treatment is ≥40% and will be evaluated using a one-sided type I error rate of 0.025 with 80% power. After evaluating the first 7 subjects for efficacy in Stage 1 in a dosing cohort, the dosing cohort will be terminated if <2 subjects respond (either CR or PR). If the dosing cohort progresses to Stage 2, an additional 11 subjects will be treated, for a total of up to 18 evaluable subjects. If at least 5 subjects respond out of the total 18, there will be demonstration of efficacy of ONCT-808 at that dose level and the corresponding null hypothesis will be rejected. Additional subjects may be enrolled to account for unevaluable subjects. The estimated maximum sample size is 24 per disease subtype.

9.2. Populations for Analysis

The DLT Evaluable Population is defined as all subjects in the Phase 1 Dose Escalation part of the study who received ONCT-808 and either completed the 28-day DLT observation period or discontinued the study early due to a DLT. Subjects will be grouped by the dose cohort received.

The Safety Population is defined as all subjects who received any study procedure or treatment post-Screening, including leukapheresis, lymphodepletion (as necessary), and ONCT-808. Subjects will be grouped by the ONCT-808 dose level assigned. Subjects who did not receive ONT-808 will be grouped separately.

The Efficacy-evaluable Population is defined as all subjects who received ONCT-808 and completed at least 1 post-treatment disease assessment and did not discontinue due to clinical evidence of disease progression or toxicity prior to obtaining at least 1 post-treatment disease assessment. Subjects will be grouped by dose level assigned.

Additional populations may be defined in the study Statistical Analysis Plan (SAP).

9.3. Statistical Analyses

9.3.1. Statistical Hypotheses

Phase 1 Dose Escalation will proceed following a 3+3 study design to determine the MTD, MAD, and/or RP2D. No hypothesis testing will be performed on Phase 1.

For each Phase 2 dose level-specific expansion cohort, up to 18 evaluable subjects will be enrolled in a Simon 2-stage design. The hypothesized response rate under treatment is ≥40% and will be evaluated using a one-sided type I error rate of 0.025 with 80% power to exclude an ORR

<10%. After evaluating the first 7 subjects for efficacy in Stage 1, the dosing cohort will be terminated if <2 subjects respond (either CR or PR). If at least 2 subjects achieve CR or PR 2 months following treatment, the cohort will progress to Stage 2 and an additional 11 subjects will be treated, for a total of up to 18 evaluable subjects. If at least 5 subjects respond out of the total 18, there will be demonstration of efficacy of the novel product within that dose level-specific cohort and the corresponding null hypothesis will be rejected.

9.4. Statistical Analysis Methods

Details of the statistical analyses will be fully described in a separate SAP to be finalized prior to the planned analyses.

Subjects will be randomized in a 1:1 allocation to 1 of the 2 dose levels, stratified by lymphoma subtype (MCL or LBCL), using block randomization with a block size of 2.

All collected data will be reported using summary tables and figures, as appropriate. Tabulations will be produced for disposition, demographic, baseline, efficacy, safety, and T-cell activation parameters. Summaries will be grouped by dose level in Phase 1 and dose level cohort in Phase 2. Categorical variables will be summarized by frequency distributions (number and percentage of subjects) and continuous variables will be summarized by descriptive statistics (mean, standard deviation, median, minimum, and maximum). For time to event variables, percentages of subjects experiencing the event will be presented and median time to event will be estimated using Kaplan-Meier methodology. As appropriate, 95% confidence intervals (CIs) will be presented.

No type I error adjustments for multiple testing are planned. No hypothesis testing will be performed on secondary endpoints.

9.5. Analysis of the Primary Endpoints

9.5.1. Analysis of the Anti-Tumor Endpoints

The ORR is defined as the proportion of efficacy-evaluable subjects with a response to treatment (defined as CR or PR). The number, percentage, and exact 95% confidence interval will be presented.

The CR Rate is defined as the proportion of efficacy-evaluable subjects with a CR to treatment. The number, percentage, and exact 95% confidence interval will be presented.

The DOR is defined as the time (in months) between initial response (CR or PR) and the date of first disease progression, relapse, or death for efficacy-evaluable subjects. DOR will be analyzed using Kaplan-Meier methods. Further detail on censoring rules will be described in the SAP.

Additional anti-tumor assessments may be summarized, as described in the SAP.

9.5.2. Safety Analyses

Safety assessments include AEs, SAEs, clinical laboratory evaluations, vital sign measurements, ECGs, concomitant medications, and exposure to study drug.

A TEAE is defined as an AE that occurs or worsens in the period from the first dose of lymphodepleting chemotherapy to the end of the post-treatment follow-up period (or

approximately 24 months after the dose of ONCT-808). TEAEs will be summarized using the Medical Dictionary for Regulatory Activities Version 13.1 (or higher) System Organ Class and Preferred Term.

The incidence and percentage of subjects experiencing each Preferred Term will be summarized. AEs will also be summarized by NCI-CTCAE, Version 5.0 and by severity and relationship to study drug. Incidence of DLTs will be reported by Preferred Term and relationship to study drug. Any Grade ≥3 AEs, SAEs, and AESIs will be summarized by Preferred Term.

Laboratory results will be classified according to NCI-CTCAE, Version 5.0. Laboratory results not corresponding to an NCI-CTCAE term will not be graded. Incidences of laboratory abnormalities will be summarized with descriptive statistics.

Vital signs and ECGs will be summarized with descriptive statistics. Concomitant medications will be listed. Exposure to study drug will be summarized.

All safety results will be reported in by-subject data listings.

9.6. Pharmacokinetic Analysis

Engraftment, expansion, persistence, and immunophenotype of ROR1 CAR-positive T cells will be summarized using descriptive statistics. Correlation analyses will be performed to assess associations between ONT-808 PK parameters and safety, and anti-tumor activity, including tumor size and best response. Additional detail will be provided in the SAP.

9.7. Baseline Descriptive Statistics

Baseline and demographic characteristics will be summarized. Additional details on the summary of disease characteristics will be presented in the study SAP.

9.8. Tabulation of Individual Subject Data

All data collected will be presented in by-subject data listings.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Regulatory, Ethical, and Oversight Considerations

10.1.1. Institutional Review Board/Ethics Committee Process

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/GCP, applicable regulatory requirements.

In obtaining and documenting informed consent during the Screening Phase, the Investigator must comply with applicable local regulatory requirements (e.g., 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56) and should adhere to ICH GCP. Prior to the beginning of the study, the Investigator should have the IRB/EC's written approval for the protocol and the written ICF(s) and any other written information to be provided to the study subjects.

The Investigator must obtain IRB/EC approval for the investigation. Initial IRB/EC approval, and all materials approved by the IRB/EC for this study, including the subject signed ICF and recruitment materials, must be maintained by the Investigator and made available for inspection.

10.1.1.1. Written Informed Consent

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. ICFs will be IRB/EC approved and the subject will be asked to read and review the document. The Investigator will explain the research study to the subject and answer any questions that may arise and will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risk, and benefit of the study. Subjects will have the opportunity to carefully review the written ICFs and ask questions prior to signing. The subjects should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The subject will sign the ICF during the Screening Phase prior to any procedures being done specifically for the study. Subjects must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the signed ICF will be given to the subjects for their records. The informed consent process will be conducted and documented in the source document (including the date), and the ICF signed, before the subject undergoes any study-specific procedures. The rights and welfare of the subjects will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

The subject's signed and dated ICF must be obtained before conducting any study procedures and prior to starting intervention or administering study intervention.

10.1.2. Study Discontinuation and Closure

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the Sponsor to the Investigator at each investigational site and the Regulatory Authority in each country where this study is being conducted. If the study is prematurely terminated or suspended, the Investigator will promptly inform study subjects, the

IRB/EC, and the Sponsor will provide the reason(s) for the termination or suspension. Study subjects will be contacted, as applicable, and be informed of changes to the study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

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

The study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the Sponsor, IRB/EC and/or Regulatory Authorities (e.g., FDA, European Medicines Agency [EMA]).

10.1.3. Confidentiality and Privacy

Subject confidentiality and privacy are strictly held in trust by the participating Investigators, their staff, and the Sponsor and their interventions. This confidentiality is extended to cover 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.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the Sponsor, representatives of the IRB/EC, or the regulatory agencies may inspect all documents and records required to be maintained by the Investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the subjects in this study. The clinical study site will permit access to such records.

The study subject's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB/EC, institutional policies, or Sponsor requirements.

Study subject research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored in a secure clinical study database. This will not include the subject contact or identifying information. Rather, individual subjects and their research data will be identified by a unique study identification number. At the end of the study, the study databases will be de-identified and archived at a secure location.

10.1.4. Safety Oversight

10.1.4.1. Safety Review Committee

Safety oversight will be the responsibility of the SRC, which is a multidisciplinary committee with the objectives to evaluate safety data, provide input and recommendations on study conduct and risk mitigation related to the following concerns:

- Are there any newly identified or potential risks with study treatment?
- Has the benefit/risk profile of ONCT-808 changed?
- Should the study be amended, paused, or stopped?
- In collaboration with Investigators, should dose escalation proceed to the next dose level?
- What is the appropriate RP2D?

The SRC is composed of the Phase 1 study Investigators, cross-functional representatives from the Sponsor, and includes at least 1 independent member with clinical and safety expertise who is not directly involved with the study. The SRC activities for this trial are described in the SRC Charter.

10.1.5. Study Monitoring

Clinical study monitoring is conducted to ensure that the rights and well-being of study subjects are protected, that the reported study data are accurate, complete, and verifiable, and that the conduct of the study is in compliance with the currently approved protocol/amendment(s), with ICH GCP, and with applicable regulatory requirement(s).

The Sponsor or designee will conduct site visits at the investigation facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, subject charts, and study source documents, and other records related to study conduct. When on-site monitoring is not possible (e.g., during a global pandemic), and where regulatory, local, and institution policies allow, remote study monitoring may be performed.

The Investigator(s)/institution(s) will permit study-related monitoring, audits, IRB/EC review, and regulatory inspection(s) by providing direct access to source data/documents to the Sponsor or their designees.

Before an investigational site can enter a subject into the study, a study monitor, on behalf of the Sponsor, will provide the Investigator and the study team training on the protocol, study drug, data collection, study procedures, safety processes, and the clinical monitoring plan.

During the study, a monitor from the Sponsor or representative will have regular contacts with the investigational site, for the following:

- Provide information and support to the Investigators.
- Confirm that facilities remain acceptable.

- Confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the eCRFs, and that study drug accountability checks are being performed.
- Perform source data verification. This includes a comparison of the data in the eCRFs with the subject's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each subject (e.g., clinic charts).
- Record and report any protocol deviations not previously sent to the Sponsor or designee.
- Confirm AEs and SAEs have been properly documented in the eCRFs.
- Confirm all SAEs have been forwarded to the Sponsor and those SAEs that meet criteria for reporting have been forwarded to the IRB.

The monitor will be available between visits if the Investigator(s) or other staff needs information or advice.

10.1.6. Quality Assurance and Quality Control

Each clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation, and completion. An individualized quality management plan will be developed to describe a site's quality management.

Following written SOPs, the monitors will verify that the clinical study is conducted; and data are generated; and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, ICH GCP, and applicable regulatory requirements (e.g., Good Laboratory Practices, Good Manufacturing Practices).

The investigational site will provide direct access to all study-related documents, source data/documents, and reports for the purpose of monitoring and auditing by the Sponsor or designees, and inspection by local and Regulatory Authorities.

Authorized representatives of the Sponsor, a Regulatory Authority, an EC, or an IRB may visit the site to perform audits or inspections, including source data verification. The purpose of a Sponsor audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP guidelines of the ICH, and any applicable regulatory requirements. The Investigator should contact the Sponsor immediately if contacted by a regulatory agency about an inspection.

The final study protocol, including the final version of the ICF, must be approved, or given a favorable opinion in writing, by an IRB or EC as appropriate. The Investigator must submit written approval to the Sponsor before he or she can enroll any patient/subject into the study.

The Investigator is responsible for informing the IRB or EC of any amendment to the protocol in accordance with local requirements. In addition, approval of all advertising used to recruit subjects for the study follow the rules of the IRB/EC and other Regulatory Authorities, if appropriate. Protocol amendment approval by the IRB/EC is required, and annually, if appropriate.

The Investigator is also responsible for providing the IRB with reports of any reportable serious adverse drug reactions from any other study conducted with the study drug. The Sponsor will provide this information to the Investigator.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB or EC according to local regulations and guidelines.

10.1.7. Data Handling and Record Keeping

10.1.7.1. Data Collection and Management Responsibilities

Data collection is the responsibility of the clinical study staff at the site under the supervision of the site Investigator. The Investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Data recorded in the eCRF derived from source documents should be consistent with the data recorded on the source documents.

Clinical data (including AEs, concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into a 21 CFR Part 11-compliant data capture system provided by the Sponsor or designee. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

10.1.7.2. Study Records Retention

Study documents should be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study intervention. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the Sponsor, if applicable. It is the responsibility of the Sponsor to inform the Investigator when these documents no longer need to be retained.

10.1.8. Protocol Deviations

A protocol deviation is any noncompliance with the clinical study protocol ICH GCP. The noncompliance may be either on the part of the subject, the Investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

All deviations must be addressed in study source documents and reported to the Sponsor or designee as per agreed communication channels. Protocol deviations must be sent to the reviewing IRB/EC per their policies. The site Investigator is responsible for knowing and adhering to the reviewing IRB/EC requirements.

10.2. Financial Disclosure

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate Health Authorities.

Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.3. Publication Policy

All information concerning ONCT-808, including but not limited to, Sponsor operations, patent applications, formulas, manufacturing processes, scientific data, and formulation information, supplied to the Investigator by a Sponsor representative and not previously published, is considered confidential and remains the sole property of the Sponsor. The Investigator must agree to use this information solely for the purposes of carrying out this study and must not use it for other purposes without the Sponsor's advanced written consent.

The information developed in this study will be used by the Sponsor in connection with the continued development of ONCT-808 and thus may be disclosed to other clinical Investigators or government regulatory agencies. The Investigator is obligated to provide the Sponsor with all data obtained in the study.

11. REFERENCES

Abramson JS, Palomba ML, Gordon LI, et al. Lisocabtagene maraleucel for patients with relapsed or refractory large B-cell lymphomas (TRANSCEND NHL 001): a multicentre seamless design study. Lancet. 2020;396(10254):839-852. doi:10.1016/S0140-6736(20)31366-0

Al-Shawi R, Ashton SV, Underwood C, Simons JP. Expression of the Ror1 and Ror2 receptor tyrosine kinase genes during mouse development. Dev Genes Evol. 2001;211(4):161-171. doi:10.1007/s004270100140

Balakrishnan A, Goodpaster T, Randolph-Habecker J, et al. Analysis of ROR1 Protein Expression in Human Cancer and Normal Tissues. Clin Cancer Res. 2017;23(12):3061-3071. doi:10.1158/1078-0432.CCR-16-2083

Barna G, Mihalik R, Timár B, et al. ROR1 expression is not a unique marker of CLL. Hematol Oncol. 2011;29(1):17-21. doi:10.1002/hon.948

Baskar S, Kwong KY, Hofer T, et al. Unique cell surface expression of receptor tyrosine kinase ROR1 in human B-cell chronic lymphocytic leukemia. Clin Cancer Res. 2008;14(2):396-404. doi:10.1158/1078-0432.CCR-07-1823

Bishop MR, Dickinson M, Purtill D, et al. Second-Line Tisagenlecleucel or Standard Care in Aggressive B-Cell Lymphoma. N Engl J Med. 2022;386(7):629-639. doi:10.1056/NEJMoa2116596

Breyanzi [package insert]. Bothell, WA: Juno Therapeutics, Inc., a Bristol Meyers Squibb Company. https://packageinserts.bms.com/pi/pi_breyanzi.pdf. Published June 2022. Accessed July 19, 2022.

Broome HE, Rassenti LZ, Wang HY, Meyer LM, Kipps TJ. ROR1 is expressed on hematogones (non-neoplastic human B-lymphocyte precursors) and a minority of precursor-B acute lymphoblastic leukemia. Leuk Res. 2011;35(10):1390-1394. doi:10.1016/j.leukres.2011.06.021

Caraballo C, Desai NR, Mulder H, et al. Clinical Implications of the New York Heart Association Classification. J Am Heart Assoc. 2019;8(23):e014240. doi:10.1161/JAHA.119.014240

Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol. 2014;32(27):3059-3068. doi:10.1200/JCO.2013.54.8800

Chien HP, Ueng SH, Chen SC, et al. Expression of ROR1 has prognostic significance in triple negative breast cancer. Virchows Arch. 2016;468(5):589-595. doi:10.1007/s00428-016-1911-3

Choi MY, Widhopf GF 2nd, Ghia EM, et al. Phase I Trial: Cirmtuzumab Inhibits ROR1 Signaling and Stemness Signatures in Patients with Chronic Lymphocytic Leukemia. Cell Stem Cell. 2018;22(6):951-959.e3. doi:10.1016/j.stem.2018.05.018

Choi MY, Widhopf GF 2nd, Wu CC, et al. Pre-clinical Specificity and Safety of UC-961, a First-In-Class Monoclonal Antibody Targeting ROR1. Clin Lymphoma Myeloma Leuk. 2015;15 Suppl(0):S167-S169. doi:10.1016/j.clml.2015.02.010

Crump M, Neelapu SS, Farooq U, et al. Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study [published correction appears in Blood. 2018 Feb 1;131(5):587-588]. Blood. 2017;130(16):1800-1808. doi:10.1182/blood-2017-03-769620

Cui B, Ghia EM, Chen L, et al. High-level ROR1 associates with accelerated disease progression in chronic lymphocytic leukemia. Blood. 2016;128(25):2931-2940. doi:10.1182/blood-2016-04-712562

Cui B, Zhang S, Chen L, et al. Targeting ROR1 inhibits epithelial-mesenchymal transition and metastasis. Cancer Res. 2013;73(12):3649-3660. doi:10.1158/0008-5472.CAN-12-3832

Daneshmanesh AH, Mikaelsson E, Jeddi-Tehrani M, et al. Ror1, a cell surface receptor tyrosine kinase is expressed in chronic lymphocytic leukemia and may serve as a putative target for therapy. Int J Cancer. 2008;123(5):1190-1195. doi:10.1002/ijc.23587

Daneshmanesh AH, Porwit A, Hojjat-Farsangi M, et al. Orphan receptor tyrosine kinases ROR1 and ROR2 in hematological malignancies. Leuk Lymphoma. 2013;54(4):843-850. doi:10.3109/10428194.2012.731599

Dave H, Anver MR, Butcher DO, et al. Restricted cell surface expression of receptor tyrosine kinase ROR1 in pediatric B-lineage acute lymphoblastic leukemia suggests targetability with therapeutic monoclonal antibodies. PLoS One. 2012;7(12):e52655. doi:10.1371/journal.pone.0052655

Flowers CR, Sinha R, Vose JM. Improving outcomes for patients with diffuse large B-cell lymphoma. CA Cancer J Clin. 2010;60(6):393-408. doi:10.3322/caac.20087

Forrester WC, Dell M, Perens E, Garriga G. A C. elegans Ror receptor tyrosine kinase regulates cell motility and asymmetric cell division. Nature. 1999;400(6747):881-885. doi:10.1038/23722

Fukuda T, Chen L, Endo T, et al. Antisera induced by infusions of autologous Ad-CD154-leukemia B cells identify ROR1 as an oncofetal antigen and receptor for Wnt5a. Proc Natl Acad Sci U S A. 2008;105(8):3047-3052. doi:10.1073/pnas.0712148105

Gentile A, Lazzari L, Benvenuti S, Trusolino L, Comoglio PM. Ror1 is a pseudokinase that is crucial for Met-driven tumorigenesis. Cancer Res. 2011;71(8):3132-3141. doi:10.1158/0008-5472.CAN-10-2662

Ghaderi A, Daneshmanesh AH, Moshfegh A, et al. ROR1 Is Expressed in Diffuse Large B-Cell Lymphoma (DLBCL) and a Small Molecule Inhibitor of ROR1 (KAN0441571C) Induced Apoptosis of Lymphoma Cells. Biomedicines. 2020;8(6):170. Published 2020 Jun 23. doi:10.3390/biomedicines8060170

Hudecek M, Lupo-Stanghellini MT, Kosasih PL, et al. Receptor affinity and extracellular domain modifications affect tumor recognition by ROR1-specific chimeric antigen receptor T cells. Clin Cancer Res. 2013;19(12):3153-3164. doi:10.1158/1078-0432.CCR-13-0330

Hudecek M, Schmitt TM, Baskar S, et al. The B-cell tumor-associated antigen ROR1 can be targeted with T cells modified to express a ROR1-specific chimeric antigen receptor. Blood. 2010;116(22):4532-4541. doi:10.1182/blood-2010-05-283309

Ida L, Yamaguchi T, Yanagisawa K, et al. Receptor tyrosine kinase-like orphan receptor 1, a target of NKX2-1/TTF-1 lineage-survival oncogene, inhibits apoptosis signal-regulating kinase

1-mediated pro-apoptotic signaling in lung adenocarcinoma. Cancer Sci. 2016;107(2):155-161. doi:10.1111/cas.12858

Jain MD, Zhao H, Wang X, et al. Tumor interferon signaling and suppressive myeloid cells are associated with CAR T-cell failure in large B-cell lymphoma. Blood. 2021;137(19):2621-2633. doi:10.1182/blood.2020007445

Janovska P, Poppova L, Plevova K, et al. Autocrine Signaling by Wnt-5a Deregulates Chemotaxis of Leukemic Cells and Predicts Clinical Outcome in Chronic Lymphocytic Leukemia. Clin Cancer Res. 2016;22(2):459-469. doi:10.1158/1078-0432.CCR-15-0154

Jiang Q, Isquith J, Ladel L, et al. Inflammation-driven deaminase deregulation fuels human pre-leukemia stem cell evolution. Cell Rep. 2021;34(4):108670. doi:10.1016/j.celrep.2020.108670

Karvonen H, Perttilä R, Niininen W, Barker H, Ungureanu D. Targeting Wnt signaling pseudokinases in hematological cancers. Eur J Haematol. 2018;101(4):457-465. doi:10.1111/ejh.13137

Katoh M, Katoh M. Comparative genomics on ROR1 and ROR2 orthologs. Oncol Rep. 2005;14(5):1381-1384. doi:10.3892/or.14.5.1381

King C, Ilic A, Koelsch K, Sarvetnick N. Homeostatic expansion of T cells during immune insufficiency generates autoimmunity. Cell. 2004;117(2):265-277. doi:10.1016/s0092-8674(04)00335-6

Klebanoff CA, Khong HT, Antony PA, Palmer DC, Restifo NP. Sinks, suppressors and antigen presenters: how lymphodepletion enhances T cell-mediated tumor immunotherapy [published correction appears in Trends Immunol. 2005 Jun;26(6):298]. Trends Immunol. 2005;26(2):111-117. doi:10.1016/j.it.2004.12.003

Kotašková J, Pavlová Š, Greif I, et al. ROR1-based immunomagnetic protocol allows efficient separation of CLL and healthy B cells. Br J Haematol. 2016;175(2):339-342. doi:10.1111/bjh.13848

Kymriah [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation. https://www.novartis.us/sites/www.novartis.us/files/kymriah.pdf. Published May 2022. Accessed July 19, 2022.

Lee DW, Santomasso BD, Locke FL, et al. ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells. Biol Blood Marrow Transplant. 2019;25(4):625-638. doi:10.1016/j.bbmt.2018.12.758

Leukemia and Lymphoma Society. Treatment for aggressive NHL subtypes. The Leukemia and Lymphoma Society® (LLS) (https://www.lls.org/lymphoma/non-hodgkin-lymphoma/nhl-subtypes/treatment-aggressive-nhl-subtypes). Accessed 19 August 2022.

Li P, Harris D, Liu Z, Liu J, Keating M, Estrov Z. Stat3 activates the receptor tyrosine kinase like orphan receptor-1 gene in chronic lymphocytic leukemia cells. PLoS One. 2010;5(7):e11859. Published 2010 Jul 29. doi:10.1371/journal.pone.0011859

Liu D, Gunther K, Enriquez LA, et al. ROR1 is upregulated in endometrial cancer and represents a novel therapeutic target [published correction appears in Sci Rep. 2022 Jun 28;12(1):10918]. Sci Rep. 2020;10(1):13906. Published 2020 Aug 17. doi:10.1038/s41598-020-70924-z

Liu Y, Yang H, Chen T, et al. Silencing of Receptor Tyrosine Kinase ROR1 Inhibits Tumor-Cell Proliferation via PI3K/AKT/mTOR Signaling Pathway in Lung Adenocarcinoma. PLoS One. 2015;10(5):e0127092. Published 2015 May 15. doi:10.1371/journal.pone.0127092

Locke FL, Neelapu SS, Bartlett NL, et al. Phase 1 Results of ZUMA-1: A Multicenter Study of KTE-C19 Anti-CD19 CAR T Cell Therapy in Refractory Aggressive Lymphoma. Mol Ther. 2017;25(1):285-295. doi:10.1016/j.ymthe.2016.10.020

Lyashenko N, Weissenböck M, Sharir A, Erben RG, Minami Y, Hartmann C. Mice lacking the orphan receptor ror1 have distinct skeletal abnormalities and are growth retarded. Dev Dyn. 2010;239(8):2266-2277. doi:10.1002/dvdy.22362

Mao Y, Xu L, Wang J, et al. ROR1 associates unfavorable prognosis and promotes lymphoma growth in DLBCL by affecting PI3K/Akt/mTOR signaling pathway. Biofactors. 2019;45(3):416-426. doi:10.1002/biof.1498

Masiakowski P, Carroll RD. A novel family of cell surface receptors with tyrosine kinase-like domain. J Biol Chem. 1992;267(36):26181-26190.

Matsuda T, Nomi M, Ikeya M, et al. Expression of the receptor tyrosine kinase genes, Ror1 and Ror2, during mouse development. Mech Dev. 2001;105(1-2):153-156. doi:10.1016/s0925-4773(01)00383-5

Morton LM, Wang SS, Devesa SS, Hartge P, Weisenburger DD, Linet MS. Lymphoma incidence patterns by WHO subtype in the United States, 1992-2001. Blood. 2006;107(1):265-276. doi:10.1182/blood-2005-06-2508

National Cancer Institute U.S. Department of Health And Human Services. Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. Published: November 27, 2017.

National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Prevention and Treatment of Cancer-Related Infections Version 1.2022. June 2, 2022.

O'Connell MP, Marchbank K, Webster MR, et al. Hypoxia induces phenotypic plasticity and therapy resistance in melanoma via the tyrosine kinase receptors ROR1 and ROR2. Cancer Discov. 2013;3(12):1378-1393. doi:10.1158/2159-8290.CD-13-0005

Oishi I, Takeuchi S, Hashimoto R, et al. Spatio-temporally regulated expression of receptor tyrosine kinases, mRor1, mRor2, during mouse development: implications in development and function of the nervous system. Genes Cells. 1999;4(1):41-56. doi:10.1046/j.1365-2443.1999.00234.x

Paganoni S, Bernstein J, Ferreira A. Ror1-Ror2 complexes modulate synapse formation in hippocampal neurons. Neuroscience. 2010;165(4):1261-1274. doi:10.1016/j.neuroscience.2009.11.056

Prussak CE, Oh C, Lujan JV, et al. Preclinical evaluation of anti-ROR1 CAR T-cells employing a ROR1 binding scFv derived from the clinical stage mAb cirmtuzumab. Poster presented at: 2020 ASCO-SITC Clinical Immuno-Oncology Symposium; February 2020; Orlando, FL.

Rottman JB, Ganley K, Eng F, et al. ROR-1 directed chimeric antigen receptor T cell recognition of self-antigen is associated with acute toxicity, T cell dysfunction, and poor tumor control. Poster presented at: 59th ASH Annual Meeting & Exposition; December 2017; Philadelphia, PA.

Sant M, Allemani C, Tereanu C, et al. Incidence of hematologic malignancies in Europe by morphologic subtype: results of the HAEMACARE project [published correction appears in Blood. 2011 Mar 24;117(12):3477]. Blood. 2010;116(19):3724-3734. doi:10.1182/blood-2010-05-282632

Sehn LH, Herrera AF, Flowers CR, et al. Polatuzumab Vedotin in Relapsed or Refractory Diffuse Large B-Cell Lymphoma. J Clin Oncol. 2020;38(2):155-165. doi:10.1200/JCO.19.00172

Specht JM, Lee S, Turtle CJ, et al. Abstract CT131: A phase I study of adoptive immunotherapy for advanced ROR1+ malignancies with defined subsets of autologous T cells expressing a ROR1-specific chimeric antigen receptor (ROR1-CAR). Cancer Res. 2018;78(Supp 13):CT131. doi.org/10.1158/1538-7445.AM2018-CT131

Srivastava S, Furlan SN, Jaeger-Ruckstuhl CA, et al. Immunogenic Chemotherapy Enhances Recruitment of CAR-T Cells to Lung Tumors and Improves Antitumor Efficacy when Combined with Checkpoint Blockade. Cancer Cell. 2021;39(2):193-208.e10. doi:10.1016/j.ccell.2020.11.005

Swerdlow SH, Campo E, Harris NL, Jaffe ES, et al., eds. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. 2008, 4th ed., Vol 2. ISBN: 978-92-832-4494-3

Tecartus [package insert]. Santa Monica CA: Kite Pharma, Inc. https://www.gilead.com/-/media/files/pdfs/medicines/oncology/tecartus/tecartus-pi.pdf. Published October 2021. Accessed July 19, 2022.

Tey SK. Adoptive T-cell therapy: adverse events and safety switches. Clin Transl Immunology. 2014;3(6):e17. Published 2014 Jun 20. doi:10.1038/cti.2014.11

Turtle CJ, Hanafi LA, Berger C, et al. Immunotherapy of non-Hodgkin's lymphoma with a defined ratio of CD8+ and CD4+ CD19-specific chimeric antigen receptor-modified T cells. Sci Transl Med. 2016;8(355):355ra116. doi:10.1126/scitranslmed.aaf8621

Uhrmacher S, Schmidt C, Erdfelder F, et al. Use of the receptor tyrosine kinase-like orphan receptor 1 (ROR1) as a diagnostic tool in chronic lymphocytic leukemia (CLL). Leuk Res. 2011;35(10):1360-1366. doi:10.1016/j.leukres.2011.04.006

Wang M, Barrientos JC, Furman RR, et al. VLS-101, a ROR1-targeting antibody-drug conjugate, demonstrates a predictable safety profile and clinical efficacy in patients with heavily pretreated mantle cell lymphoma and diffuse large B-cell lymphoma. Blood. 2020;136 (Supp 1): 13–14. doi.org/10.1182/blood-2020-136373

Wang M, Barrientos JC, Furman RR, et al. Zilovertamab Vedotin Targeting of ROR1 as Therapy for Lymphoid Cancers. NEJM Evid 2022; 1 (1).

Widhopf GF 2nd, Cui B, Ghia EM, et al. ROR1 can interact with TCL1 and enhance leukemogenesis in Eμ-TCL1 transgenic mice. Proc Natl Acad Sci U S A. 2014;111(2):793-798. doi:10.1073/pnas.1308374111

Yamaguchi T, Yanagisawa K, Sugiyama R, et al. NKX2-1/TITF1/TTF-1-Induced ROR1 is required to sustain EGFR survival signaling in lung adenocarcinoma. Cancer Cell. 2012;21(3):348-361. doi:10.1016/j.ccr.2012.02.008

Yescarta [package insert]. Santa Monica, CA: Kite Pharma, Inc. https://www.gilead.com/-/media/files/pdfs/medicines/oncology/yescarta/yescarta-pi.pdf. Published April 2022. Accessed July 19, 2022.

Yoda A, Oishi I, Minami Y. Expression and function of the Ror-family receptor tyrosine kinases during development: lessons from genetic analyses of nematodes, mice, and humans. J Recept Signal Transduct Res. 2003;23(1):1-15. doi:10.1081/rrs-120018757

Yu J, Chen Y, Chen L, et al. Cirmtuzumab inhibits ibrutinib-resistant, Wnt5a-induced Rac1 activation and proliferation in mantle cell lymphoma. Oncotarget. 2018;9(37):24731-24736. Published 2018 May 15. doi:10.18632/oncotarget.25340

Zhang S, Chen L, Cui B, et al. ROR1 is expressed in human breast cancer and associated with enhanced tumor-cell growth. PLoS One. 2012;7(3):e31127. doi:10.1371/journal.pone.0031127

Zhang S, Cui B, Lai H, et al. Ovarian cancer stem cells express ROR1, which can be targeted for anti-cancer-stem-cell therapy. Proc Natl Acad Sci U S A. 2014;111(48):17266-17271. doi:10.1073/pnas.1419599111

APPENDIX 1. LUGANO CLASSIFICATION

The Lugano 2014 revised criteria for response assessment in lymphoma (Cheson, 2014) are presented below.

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* with or without a residual mass on 5PS†	Target nodes/nodal masses must regress to ≤ 1.5 cm in LDi
	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	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 5† with reduced uptake compared with baseline and residual mass(es) of any size	≥ 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites
	At interim, these findings suggest responding disease	When a lesion is too small to measure on CT, assign 5 mm × 5 mm as the default value
	At end of treatment, these findings indicate residual disease	When no longer visible, 0 × 0 mm
		For a node > 5 mm × 5 mm, but smaller than normal, use actual measurement for calculation
Nonmeasured lesions	Not applicable	Absent/normal, regressed, but no increase
Organ enlargement	Not applicable	Spleen must have regressed by > 50% in length beyond normal
New lesions	None	None
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 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 lesions	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 disease	Progressive disease requires at least 1 of the following
Individual target nodes/nodal masses	Score 4 or 5 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

(continued on following page)

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; 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 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 de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid undertreatment). Measured dominant lesions: Up to six 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, 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).

†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.

APPENDIX 2. EASTERN COOPERATIVE ONCOLOGY GROUP PERFORMANCE STATUS

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

APPENDIX 3. AMERICAN SOCIETY FOR TRANSPLANTATION AND CELLULAR THERAPY CONSENSUS GRADING SYSTEM AND TOXICITY MANAGEMENT

Table 9: ASTCT Cytokine Release Syndrome Consensus Grading System [a]

CRS	Grade 1	Grade 2	Grade 3	Grade 4
Fever [b]	Temperature ≥38˚C	Temperature ≥38˚C	Temperature ≥38˚C	Temperature ≥38˚C
With either:				
Hypotension	None	Not requiring vasopressors	Requiring vasopressors with/without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
And/or [c]				
Hypoxia	None	Requiring low-flow nasal cannula [d] or blow-by	Requiring high-flow nasal cannula, facemask, non-rebreather mask, or venturi mask	Requiring positive pressure (e.g., CPAP, BiPAP, intubation and mechanical ventilation)

ASTCT, American Society for Transplantation and Cellular Therapy; BiPAP, bilevel positive airway pressure; CPAP, continuous positive airway pressure; CRS, cytokine release syndrome; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events.

[a] Organ toxicities associated with CRS may be graded according to NCI-CTCAE v5.0, but they do not influence CRS grading.

[b] Fever is defined as temperature ≥38°C not attributable to any other cause. Constitutional symptoms of CRS, such as myalgia, arthralgia, and malaise, are by themselves nonspecific; however, when coincident with fever in the expected timeframe, the etiology of CRS is more likely. In subjects who have CRS then receive antipyretics or anti-cytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.

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

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

Source: Lee, 2019.

APPENDIX 4. ASTCT IMMUNE EFFECTOR CELL-ASSOCIATED NEUROTOXICITY SYNDROME GRADING

Table 10: ASTCT Immune Effector Cell-Associated Neurotoxicity Syndrome Grading[a]

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE Score [b]	7 to 9	3 to 6	0 to 2	0 (Subject is unarousable and unable to perform ICE.)
Depressed level of consciousness [c]	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Subjects is unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma.
Seizure	NA	NA	Any clinical seizure Focal/generalized that resolves rapidly; or nonconvulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (≥5 minutes); or Repetitive clinical or electrical seizures without return to baseline in between.
Motor Findings [d]	NA	NA	NA	Deep focal motor weakness such as hemiparesis or paraparesis.
Raised ICP/ Cerebral Edema	NA	NA	Focal/local edema on neuroimaging [e]	Diffuse cerebral edema on neuroimaging; Decerebrate or Decorticate posturing; or Cranial nerve VI palsy; or Papilledema; or Cushing's triad.

ASTCT, American Society for Transplantation and Cellular Therapy; ICANS, immune effector cell-associated neurotoxicity syndrome; ICE, Immune Effector Cell-Associated Encephalopathy (score); ICP, intracranial pressure; EEG, electroencephalogram; NA, not applicable; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events.

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

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

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

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

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

Source: Lee, 2019.