

Protocol

Protocol for: Bishop MR, Dickinson M, Purtill D, et al. Second-Line tisagenlecleucel or standard care in aggressive B-cell lymphoma. N Engl J Med 2022;386:629-39. DOI: 10.1056/NEJMoa2116596

This trial protocol has been provided by the authors to give readers additional information about the work.

This trial protocol and statistical analysis plan has been provided by the authors to give reviewers additional information about their work. Protocol and SAP for: *Tisagenlecleucel Versus Standard of Care in Second-Line Aggressive B-Cell Lymphoma*

This supplement contains the following items:

1. Original protocol, final protocol, summary of changes
2. Original statistical analysis plan, final statistical analysis plan, summary of changes

Novartis Research and Development

CTL019, tisagenlecleucel, Kymriah[®]

Clinical Trial Protocol CCTL019H2301

**Tisagenlecleucel versus standard of care in adult patients
with relapsed or refractory aggressive B-cell non-Hodgkin
lymphoma: A randomized, open label, phase III trial
(BELINDA)**

Document type: Oncology Clinical Trial Protocol

EUDRACT number: 2016-002966-29

Version number: 00 (Original Protocol)

Development phase: III

Document status: Final

Release date: 12-Jun-2018

Property of Novartis

Confidential

May not be used, divulged, published, or otherwise disclosed
without the consent of Novartis

Clinical Trial Protocol Template Version 1.0 (01-Dec-2017)

Table of contents

Table of contents	2
List of tables	7
List of figures	8
List of abbreviations	9
Glossary of terms	15
Protocol summary	17
1 Introduction	24
1.1 Background	24
1.1.1 Overview of disease pathogenesis, epidemiology and current treatment	24
1.1.2 Overview of tisagenlecleucel	29
1.2 Purpose	32
2 Objectives and endpoints	33
3 Study design	34
4 Rationale	36
4.1 Rationale for study design	36
4.2 Rationale for dose/regimen and duration of treatment	38
4.3 Rationale for choice of comparator drugs	39
4.4 Rationale for lymphodepletion	39
4.5 Purpose and timing of interim analyses	40
4.6 Risks and benefits	40
4.6.1 Identified safety risks with the use of tisagenlecleucel	41
4.6.2 Potential safety risks	45
4.6.3 Other risks	48
5 Population	49
5.1 Inclusion criteria	50
5.2 Exclusion criteria	51
6 Treatment	53
6.1 Study treatment	53
6.1.1 Investigational and control drugs	53
6.1.2 bPre-infusion evaluation	55
6.1.3 Additional safety procedures prior to tisagenlecleucel infusion	56
6.1.4 Additional study treatments	56
6.1.5 Treatment arms	58
6.1.6 Treatment duration	58

6.1.7	Dosing regimen	59
6.2	Other treatment(s)	60
6.2.1	Concomitant therapy	60
6.2.2	Prohibited concomitant medication and non-drug therapy	60
6.3	Subject numbering, treatment assignment, randomization	61
6.3.1	Subject numbering	61
6.3.2	Treatment assignment, randomization	61
6.4	Treatment blinding	62
6.5	Dose modification	62
6.5.1	Follow-up for toxicities	62
6.6	Additional treatment guidance	64
6.6.1	Treatment compliance	64
6.6.2	Recommended treatment for adverse events	64
6.7	Preparation and dispensation	71
6.7.1	Handling of study treatment and additional treatment	71
7	Informed consent procedures	72
8	Visit schedule and assessments	72
8.1	Screening	95
8.1.1	Eligibility screening	97
8.1.2	Information to be collected on screening failures	97
8.2	Subject demographics/other baseline characteristics	98
8.3	Efficacy	98
8.3.1	Transmission of efficacy data to BIRC	101
8.3.2	Non-expedited review - timepoints without locally determined progression or stable disease	102
8.3.3	Expedited review - timepoints with locally determined progression or stable disease	102
8.4	Safety	103
8.4.1	Laboratory evaluations	104
8.4.2	Electrocardiogram (ECG)	105
8.4.3	Pregnancy	107
8.4.4	Spirometry	107
8.4.5	Other safety evaluations	107
8.4.6	Appropriateness of safety measurements	108
8.5	Additional assessments	108
8.5.1	Patient reported outcomes (PRO)	108
8.5.2	Pharmacokinetics	111

8.5.3	Biomarkers	122
8.5.4	Imaging	126
8.5.5	Survival follow-up	126
8.5.6	Other assessments	126
9	Study discontinuation and completion	126
9.1	Discontinuation.....	126
9.1.1	Discontinuation of study treatment	126
9.1.2	Criteria for premature patient discontinuation from the study.....	127
9.1.3	Withdrawal of informed consent.....	128
9.1.4	Lost to follow-up.....	129
9.1.5	Early study termination by the sponsor.....	129
9.1.6	Criteria for stopping or pausing the study	129
9.2	Study completion and post-study treatment	130
10	Safety monitoring and reporting.....	131
10.1	Definition of adverse events and reporting requirements.....	131
10.1.1	Adverse events	131
10.1.2	Serious adverse events	134
10.1.3	SAE reporting.....	135
10.1.4	Pregnancy reporting	136
10.1.5	Reporting of study treatment errors	136
10.2	Additional safety monitoring.....	137
10.2.1	Liver safety monitoring.....	137
10.2.2	Renal safety monitoring.....	138
10.2.3	Data Monitoring Committee	138
10.2.4	Steering committee.....	138
10.2.5	Blinded independent review committee (BIRC).....	138
10.2.6	Follow up of secondary malignancy	139
11	Data collection and database management.....	139
11.1	Data collection.....	139
11.2	Database management and quality control	139
11.3	Site monitoring	140
12	Data analysis and statistical methods	140
12.1	Analysis sets	141
12.1.1	Screened Set	141
12.1.2	Full Analysis Set	141
12.1.3	Safety Set	141

12.1.4	Per-Protocol Set	141
12.1.5	Pharmacokinetic analysis set.....	142
12.2	Subject demographics and other baseline characteristics	142
12.3	Treatments	142
12.4	Analysis of the primary endpoint(s)	142
12.4.1	Definition of primary endpoint(s)	143
12.4.2	Statistical model, hypothesis, and method of analysis	143
12.4.3	Handling of missing values/censoring/discontinuations	143
12.4.4	Sensitivity and supportive analyses	144
12.5	Analysis of secondary endpoints	145
12.5.1	Efficacy and/or pharmacodynamic endpoint(s)	146
12.5.2	Safety endpoints	146
12.5.3	Patient reported outcomes	150
12.5.4	Cellular kinetics	151
12.5.5	Biomarkers	152
12.5.6	Correlation of baseline rituximab levels with clinical response	154
12.5.7	Efficacy in sub-populations.....	154
12.6	Analysis of exploratory endpoints	154
12.6.1	Efficacy and safety after cross-over	154
12.6.2	Healthcare resource utilization.....	155
12.7	Interim analyses	155
12.8	Sample size calculation.....	155
12.8.1	Primary endpoint(s).....	155
13	Ethical considerations and administrative procedures	156
13.1	Regulatory and ethical compliance.....	156
13.2	Responsibilities of the investigator and IRB/IEC.....	156
13.3	Publication of study protocol and results.....	156
13.4	Quality control and quality assurance.....	156
14	Protocol adherence	157
14.1	Protocol Amendments	157
15	References	158
16	Appendices	167
16.1	Appendix 1: Eligibility based on serologic markers for hepatitis B and C:	167
16.2	Appendix 2: Guidelines for efficacy evaluation in non-Hodgkin-Lymphoma studies	168
16.2.1	Introduction	168

16.2.2	Methodologies	168
16.2.3	Definitions	169
16.2.4	Efficacy assessments	171
16.2.5	Data handling and programming conventions	183
16.2.6	Appendices	184
16.3	Appendix 3: Tisagenlecleucel modified data reporting – Treatment and Follow Up Phase.....	186
16.4	Appendix 4: Liver event and laboratory trigger definitions and follow-up requirements	187
16.5	Appendix 5: Specific renal alert criteria and actions and event follow-up.....	190

List of tables

Table 1-1	Phase III trials in relapsed/refractory DLBCL	27
Table 2-1	Objectives and related endpoints	33
Table 4-1	Clinical signs and symptoms associated with CRS (Lee et al 2014)	41
Table 6-1	Defined risk factors and risk groups of International Prognostic Index (IPI)	62
Table 6-2	CRS management.....	66
Table 6-3	High dose vasopressor use	67
Table 8-1	Visit evaluation schedule pre-screening to randomization	74
Table 8-2	Visit evaluation schedule for Arm A (patients randomized to tisagenlecleucel treatment strategy)	76
Table 8-3	Visit evaluation schedule for Arm B (patients randomized to SOC treatment strategy).....	85
Table 8-4	Visit evaluation schedule for patients who cross over from Arm B (SOC) to Arm A (tisagenlecleucel).....	88
Table 8-5	Imaging or disease assessment collection plan	101
Table 8-6	Physical assessments	103
Table 8-7	ECOG performance status grade.....	103
Table 8-8	Laboratory assessments.....	105
Table 8-9	Non compartmental cellular kinetics parameters.....	111
Table 8-10	Validated analytical methods and limit of quantification associated with the PK analytes and immunogenicity assessments	112
Table 8-11	Tisagenlecleucel cellular kinetics by qPCR in peripheral blood collection log for patients in screening to randomization, Arm A, and in patients that cross over from Arm B to Arm A.	113
Table 8-12	Tisagenlecleucel cellular kinetics by flow cytometry in peripheral blood collection log for patients in screening to randomization, and Arm A, and in patients that cross over from Arm B to Arm A.	115
Table 8-13	Tisagenlecleucel cellular kinetics by q-PCR in bone marrow aspirate collection log for patients in screening to randomization, Arm A, and for patients that cross over from Arm B to Arm A.	117
Table 8-14	Tisagenlecleucel cellular kinetics by flow cytometry in bone marrow aspirate collection log for patients in screening to randomization, Arm A, and in patients that cross over from Arm B to Arm A.	118
Table 8-15	Tisagenlecleucel cellular kinetics by q-PCR in CSF biopsy.....	118
Table 8-16	Immunogenicity serum sample collection for patients in screening to randomization, and Arm A, and in patients that cross over from Arm B to Arm A.	119

Table 8-17	Immunogenicity peripheral blood sample collection log for patients in screening to randomization, and Arm A, and in patients that cross over from Arm B to Arm A.	120
Table 8-18	Tisagenlecleucel cellular kinetics by qPCR in tocilizumab treated patients during CRS in Arm A and in patients that cross-over from Arm B to Arm A	121
Table 8-19	Rituximab PK.....	122
Table 8-20	Biomarker sample collection- peripheral blood for serum cytokine and soluble marker analyses.....	124
Table 8-21	Biomarker sample collection – B cell levels (peripheral blood).....	124
Table 8-22	Biomarker sample collection – immunophenotyping, gene expression profiling, (peripheral blood) and ctDNA plasma for MRD and tumor clonal analysis by Ig deep sequencing.....	125
Table 8-23	Sample collection - exploratory analysis on tumor biopsy	125
Table 10-1	Guidance for capturing the study treatment errors including misuse/abuse	137
Table 16-1	Eligibility based on serologic marker for hepatitis B and C	167
Table 16-2	Five Point Scale (5PS)	169
Table 16-3	Radiological response assessment.....	174
Table 16-4	Overall disease response	177
Table 16-5	Censoring reasons	181
Table 16-6	Options for event dates used in PFS, EFS, TTP, DOR	182
Table 16-7	Data reporting: adverse events, concomitant medications, and laboratory values	186
Table 16-8	Liver event and laboratory trigger definitions	187
Table 16-9	Follow up requirements for liver events and laboratory triggers	188
Table 16-10	Specific renal alert criteria and actions	190
Table 16-11	Follow up of renal events	190

List of figures

Figure 1-1	Tisagenlecleucel chimeric antigen receptor design.....	30
Figure 3-1	Study design	36

List of abbreviations

5PS	5 point scale
AAIPI	Age-adjusted international prognostic index
ABC	Activated B-cell
AE	Adverse event
AESI	Adverse events of special interest
ALC	Absolute lymphocyte count
ALK	Alkaline
ALL	Acute Lymphoblastic Leukemia
ALP	Alkaline phosphate
ALS	Amyotrophic lateral sclerosis
ALT	Alanine aminotransferase/glutamic pyruvic transaminase/SGPT
ANC	Absolute neutrophil count
aPTT	Activated partial thromboplastin time
ASH	American Society of Hematology
ASCT	Autologous stem cell transplant
AST	Aspartate aminotransferase/glutamic oxaloacetic transaminase/SGOT
ATC	Anatomical therapeutic chemical
ATG	Anti-thymocyte globulin
AUC	Area under the curve
AV block	Atrioventricular block
B-ALL	B-cell acute lymphoblastic leukemia
Bcl-2	B-cell lymphoma 2
BEAM	Carmustine, Etoposide, Cytarabine, Melphalan
BM	Bone marrow
BOR	Best overall response
BUN	Blood Urea Nitrogen
CABG	Coronary artery bypass graft
CAR	Chimeric antigen receptor
CCG	CRF Completion Guidelines
CD19 CART	CD 19 redirected chimeric antigen receptor T cell
CDS	Core data sheet
CFR	Code of Federal Regulations
CGD	Chronic granulomatous disease
CHOP	Cyclophosphamide, doxorubicin, vincristine, prednisone
CI	Confidence Interval
CK	Cellular kinetics
CKAS	Cellular kinetic analysis set
C _{last}	Concentration last
CLL	Chronic Lymphocytic Leukemia
C _{max}	Maximum concentration
CMO&PS	Chief Medical Office and Patient Safety
CMR	Complete metabolic response
CMV	Cytomegalovirus
c-myc	c-myc proto-oncogene
CNS	Central Nervous System

CORAL	Collaborative Trial in Relapsed Aggressive Lymphoma
CR	Complete Response
CRF	Case Report/Record Form; the term CRF can be applied to either EDC or Paper
CRO	Contract research organization
CRP	C-Reactive Protein
CRS	Cytokine release syndrome
CSF	Cerebral spinal fluid
CSP	Clinical study protocol
CSR	Clinical study report
CT	Computed tomography
CTC	Common toxicity criteria
CTCAE	Common terminology criteria for adverse events
CTL	Cytotoxic T-lymphocyte
CV%	Coefficient of Variation (%)
DFS	Disease free survival
DHAP	Dexamethasone, high dose, cytarabine (Ara-C, cisplatin (platinum))
DILI	Drug induced liver injury
DLBCL	Diffuse large B-cell lymphoma
DLCO	Diffusing capacity carbon monoxide
DMC	Data monitoring committee
DNA	Deoxyribonucleic acid
DOR	Duration of Response
DRESS	Drug reaction with eosinophilia and systemic symptoms
EBV	Epstein-Barr virus
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture
EDTA	Ethylenediaminetetraacetic acid
EEG	Electroencephalography
EFS	Event free survival
eGFR	Estimated Glomerular Filtration Rate
ePRO	Electronic patient reported outcome
ELISA	Enzyme-linked immunosorbent assay
EQ-VAS	EuroQoL visual analogue scale
EQ-5D	EuroQoL 5 dimensions
EMA	European Medicines Agency
EOS	End of study
ESMO	European Society for Medical Oncology
EU	European Union
EWB	Emotional Well-Being
FACT-G	Functional assessment of cancer therapy general
FACT-Lym	Functional assessment of cancer therapy lymphoma
FACT-LymS	Functional assessment of cancer therapy lymphoma subscale
FACT-TOI	Functional assessment of cancer therapy total outcome index
FACT-TS	Functional assessment of cancer therapy total score

FAS	Full analysis set
FDA	Food & Drug Administration
FDG	Fluorodeoxyglucose
FEV1	Forced expiratory volume in one second
FFPE	Formalin-fixed paraffin-embedded
FH	Fleming-Harrington
FISH	Fluorescence in situ hybridization
FL	Follicular lymphoma
FNA	Fine needle aspirate
FPFV	First Patient First Visit
FWB	Functional well-being
GBS	Guillain-Barre syndrome
GCB	Germinal center B-cell
GCP	Good Clinical Practice
G-CSF	Granulocyte colony stimulating factor
GDP	Gemcitabine, dexamethasone, cisplatin
GemOx	Gemcitabine, oxiplatin
GEP	Gene expression profiling
GGT	Gamma glutanyl transferase
GI	Gastrointestinal
GM-CSF	Granulocyte macrophage-colony stimulating factor
GVHD	Graft versus host disease
HBcAb	Hepatitis B core antibody
HBsAb	Hepatitis B surface antibody
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HDCT	High dose chemotherapy
HIV	Human immunodeficiency virus
HLA	Histocompatibility antigens
HR	Hazard ratio
HRQoL	Health related quality of life
HSC	Hematopoietic stem cell
HSCT	Hematopoietic stem cell transplantation (refers to both allogenic SCT and autologous SCT)
HSV	Herpes simplex virus
i.v.	Intravenous(ly)
IB	Investigator's brochure
ICE	Ifosfamide, carboplatin, etoposide
ICF	Informed consent form
ICH	International Council on Harmonization
ICU	Intensive care unit
IDO	Indoleamine 2,3-dioxygenase
IEC	Independent ethics committee
IFN-g	Interferon gamma
Ig	Immunoglobulin
IHC	Immunohistochemistry
IL	Interleukin

IL6R	Interleukin 6 receptor
IMP	Investigational medicinal product
IN	Investigator notification
INR	International normalized ratio
IPI	International prognostic index
IRB	Institutional Review Board
BIRC	Blinded Independent Review Committee
IRT	Interactive response technology
IT	Intrathecal
ITP	Autoimmune thrombocytopenia/thrombocytopenic purpura
ITT	Intent to treat
IUD	Intrauterine device
IUS	Intrauterine System
IWRS	Interactive web response system
JC	John Cunningham (virus)
LD	Lympho depletion
LDH	Lactate dehydrogenase
LDi	Longest diameter
LFT	Liver function tests
LISA	Lentivirus insertion site analysis
LLOQ	Lower limit of quantification
LPLV	Last Patient Last Visit
LSS	Lymphoma specific survival
LTFU	Long Term Follow Up
LTR	Long terminal repeat
LVEF	Left ventricular ejection fraction
MAS	Macrophage activation syndrome
MCHC	Mean corpuscular hemoglobin concentration
MCS	Mental component summary
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MHC	Major histocompatibility complex
MMc	Maternal microchimerism
mPFS	Median progression free survival
MRA	Magnetic resonance angiography
MRD	Minimum residual disease
MRI	Magnetic resonance imaging
MUGA	Multigated acquisition
NCCN	National Comprehensive Cancer Network
NCIC-CTG	National Cancer Institute of Canada Clinical Trials Group
NE	Norepinephrine equivalent
NGS	Next generation sequencing
NHL	Non-Hodgkin's Lymphoma
NK	Natural killer cell
NMR	No metabolic response
NOS	Not otherwise specified
NYHA	New York Heart Association

ORR	Overall response rate
OS	Overall survival
PAS	Pharmacokinetic analysis set
PB	Peripheral blood
PBMC	Peripheral blood mononuclear cells
PCR	Polymerase Chain Reaction
PCS	Physical component summary
PD	Progressive disease or Pharmacodynamics
PD1	Programmed cell death 1
PDL1	Programmed death ligand 1
PET	Positron emission tomography
PFS	Progression free survival
PK	Pharmacokinetics
PMBCL	Primary mediastinal B-cell lymphoma
PMD	Progressive metabolic disease
PML	Progressive multifocal leukoencephalopathy
PMR	Partial metabolic response
PPD	Perpendicular diameter
PPS	Per-protocol set
PR	Partial response
PRO	Patient reported outcome
PT	Preferred term OR Prothrombin time
PTLD	Post-transplant lymphoproliferative disorders
PWB	Physical Well-Being
q12hr	Every 12 hours
QA	Quality Assurance
QMS	Quality Management System
qPCR	Quantitative polymerase chain reaction
QTcF	QT interval correction formula
R	Rituximab
r/r	Relapsed or refractory
RAP	Reporting and analysis plan
RCL	Replication competent lentivirus
RD	Relapsed disease
RNA	Ribonucleic acid
SAE	Serious Adverse Event
SAP	Statistical analysis plan
SC	Steering committee
scFv	Single chain variable fragment
SCID-X1	X-linked severe combined immunodeficiency
SCT	Stem cell transplantation
SD	Stable Disease
SDi	Shortest diameter
SF-36	Short Form 36 health survey
SGOT	Serum glutamic-oxalacetic transaminase
SGPT	Serum glutamic-pyruvic transaminase
SNP	Single nucleotide polymorphism

SOC	System organ class or Standard of care
SPD	Sum of the product of the diameters
SUSAR	Suspected unexpected serious adverse reactions
SUV	Standardized uptake value
SWB	Social well being
T _{1/2}	Time to half life
TBIL	Total bilirubin
TCR	T cell receptor
TdP	Torsades de pointes
T/HRBCL	T-cell/Histiocyte-rich B-cell Lymphoma
T _{last}	Timepoint of last measurable concentration
TLS	Tumor lysis syndrome
T _{max}	Time to peak concentration
TNF	Tumor necrosis factor
TPAS	Tocilizumab pharmacokinetic analysis set
TPR	Timepoint response
TTP	Time to progression
TTCR	Time to complete response
TTR	Time to response
ULN	Upper limit of normal
UNK	Unknown
US	Ultrasound
USPI	United States Prescribing Information
V _H	Heavy Chain Variable Domain
V _L	Light Chain Variable Domain
VSV	Vesicular Stomatitis Virus
VSV-G	Vesicular Stomatitis Virus/Glycoprotein
WAS	Wiskott-Aldrich syndrome
WBC	White blood cells
WHO	World Health Organization
WOCBP	Women of child bearing potential

Glossary of terms

Assessment	A procedure used to generate data required by the study
Screening (Baseline) Efficacy Assessment	The assessment is done within 4 weeks of randomization. If multiple assessments are performed then the one closest temporally to randomization will serve as baseline assessment.
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study subject or patient
(Optional) Bridging Therapy	Rituximab based therapy given prior to tisagenlecleucel infusion
Cohort	A specific group of subjects fulfilling certain criteria and generally treated at the same time
Dose level	The dose of drug given to the patient (total daily or weekly etc.)
Investigational drug	The study treatment whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with "investigational new drug."
Investigational treatment	Drug whose properties are being tested in the study as well as their associated placebo and active treatment controls (when applicable). This also includes approved drugs used outside of their indication/approved dosage, or that are tested in a fixed combination. Investigational treatment generally does not include other study treatments administered as concomitant background therapy required or allowed by the protocol when used within approved indication/dosage
Period	A subdivision of the study timeline; divides stages into smaller functional segments such as screening, baseline, titration, washout, etc.
Personal Data	Subject information collected by the Investigator that is transferred to Novartis for the purpose of the clinical trial. This data includes subject identifier information, study information and biological samples.
Premature patient withdrawal	Point/time when the patient exits from the study prior to the planned completion of all study treatment administration and/or assessments; at this time all study treatment administration is discontinued and no further assessments are planned, unless the patient will be followed for progression and/or survival
RAP	Report and analysis plan is a regulatory document which provides evidence of preplanned analyses
Randomization	Point or time when patients have met all clinical eligibility and are assigned to Arm A (optional bridging chemo + lymphodepleting chemotherapy + tisagenlecleucel) or Arm B (SOC)
Stage related to study timeline	A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, randomization, completion of treatment, etc.
Stop study participation	Point/time at which the patient came in for a final evaluation visit or when study treatment was discontinued whichever is later
Study treatment	Includes any drug or combination of drugs in any study arm administered to the patient (subject) as part of the required study procedures, including lymphodepleting chemotherapy. In specific examples, it is important to judge investigational treatment component relationship relative to a study treatment combination; study treatment in this case refers to the investigational and non-investigational treatments in combination.
Study treatment discontinuation	Point/time when a patient permanently stops taking study treatment for any reason
Subject Number	A number assigned to each subject upon signing the informed consent. This number is the definitive, unique identifier for the subject and should be used to identify the subject throughout the study for all data collected, sample labels, etc.
Variable	A measured value or assessed response that is determined from specific assessments and used in data analysis to evaluate the drug being tested in the study

Withdrawal of study consent	Withdrawal of consent from the study occurs only when a subject does not want to participate in the study any longer, and does not allow any further collection of personal data
-----------------------------	--

Protocol summary

Protocol number	CCTL019H2301
Full Title	Tisagenlecleucel versus standard of care in adult patients with relapsed or refractory aggressive B-cell non-Hodgkin lymphoma: A randomized, open label, phase III trial (BELINDA)
Brief title	Tisagenlecleucel in adult patients with aggressive B-cell non-Hodgkin lymphoma
Sponsor and Clinical Phase	Novartis - Phase III
Investigation type	Biological
Study type	Interventional
Purpose and rationale	<p>Current therapies for diffuse large B-cell lymphoma (DLBCL) and other aggressive B-cell non-Hodgkins lymphoma (NHL) (e.g. FL3B, primary mediastinal B cell lymphoma (PMBCL), T cell rich/histiocyte rich large B cell lymphoma, DLBCL associated with chronic inflammation, intravascular large B-cell lymphoma, anaplastic lymphoma kinase positive (ALK+) large B-cell lymphoma) consist of combination chemotherapies with CD20-targeted immunotherapies. While over 50% of patients reach long-lasting complete response (CR) with initial therapy, approximately one-third of patients are refractory (i.e. do not achieve a response) to therapy or will relapse or progress after initial response. These patients have poor prognosis, especially if they are refractory or have an early relapse (i.e., within 12 months of last therapy) even if the patient receives high dose chemotherapy and stem cell transplant. Novel therapies for relapsed/refractory (r/r) DLBCL and other aggressive B-cell lymphomas are highly needed.</p> <p>The B-cell marker CD19 has emerged as a target for DLBCL B-cell lymphoma treatment in the past years. It is widely expressed on normal and malignant B-cells throughout B-cell maturation but not on pluripotent stem cells or non-B-cell tissues. The vast majority of DLBCL expresses CD19 (Kimura et al 2007). Targeting CD19 by chimeric antigen receptor (CAR) T-cell therapy has been shown to be effective at eradicating malignant cells from very advanced B-cell malignancies and to have the potential to induce durable complete responses in patients lacking effective treatment options. Data from patients with B-cell Acute Lymphoblastic Leukemia (ALL), Chronic Lymphocytic Leukemia (CLL), and other CD19 expressing B cell lymphomas show that tisagenlecleucel therapy has potent anti-tumor activity.</p> <p>This phase III study will compare the efficacy and safety of tisagenlecleucel treatment strategy against the current SOC (standard second line salvage chemotherapy including autologous hematopoietic stem cell transplant (HSCT) in suitable patients), in poor prognosis patients with aggressive B-cell NHL after failure of frontline rituximab- and anthracycline-based therapy.</p> <p>The two treatment strategies being compared are</p> <ul style="list-style-type: none"> • CTL019 after optional bridging chemotherapy and lymphodepleting (LD) chemotherapy • Standard of care chemotherapy followed by transplant
Primary Objective(s)	The primary objective of this study is to compare tisagenlecleucel treatment strategy to SOC treatment strategy with respect to delaying the composite event of disease progression(PD)/stable disease (SD) at or after the Week 12 assessment; or death at any time, i.e. event free survival (EFS) as assessed by a blinded independent review committee (BIRC).

Secondary Objectives	<ul style="list-style-type: none">• To compare tisagenlecleucel treatment strategy to SOC treatment strategy with respect to EFS by local investigator.• To compare tisagenlecleucel treatment strategy to SOC treatment strategy with respect to overall survival (OS).• To compare tisagenlecleucel treatment strategy to SOC treatment strategy with respect to overall response rate (ORR) and duration of response (DOR) by BIRC and local investigator.• To evaluate safety and tolerability of tisagenlecleucel treatment strategy versus SOC treatment strategy.• To compare patient reported outcomes (PROs) of health-related quality of life (HRQoL) in both treatment arms.• Evaluate efficacy and safety of both treatment arms in histological subgroups (DLBCL, not otherwise specified (NOS), FL3B, other) and molecular subgroups (e.g. germinal center B-cell (GCB), activated B-cell (ABC), other)• To assess the patients treated with tisagenlecleucel treatment strategy with respect to the following objectives:<ul style="list-style-type: none">• Characterize the in vivo cellular kinetics (levels, expansion, persistence) of tisagenlecleucel transduced cells into target tissues (blood, bone marrow, cerebral spinal fluid (CSF) and other tissues if available)), as measured by quantitative polymerase chain reaction (qPCR) summarized by clinical response• Characterize immunogenicity including pre-existing (pre-dose) and post-tisagenlecleucel infusion in patients treated with tisagenlecleucel on cellular kinetics and efficacy• Assess presence of replication competent lentivirus (RCL) in patients receiving tisagenlecleucel.
-----------------------------	---

Study design	<p>This is a randomized, open label, multicenter phase III trial comparing the efficacy, safety, and tolerability of tisagenlecleucel to SOC in adult patients with aggressive B-cell NHL after failure of rituximab and anthracycline containing frontline immunochemotherapy. Failure of frontline therapy is defined as refractoriness (lack of response or progression during therapy) or relapse/progression within 365 days of last dose of therapy (in patients who achieved CR or partial response (PR) on frontline therapy).</p> <p>All screened patients will undergo non-mobilized leukapheresis for autologous T cell collection soon after obtaining informed consent. During the screening period, no lymphoma-specific therapy is allowed prior to randomization. During randomization, patients will be stratified by:</p> <p>(a) Remission duration - refractory or relapse \leq 6 months from last dose of first line immunochemotherapy v. 6 to 12 months) and</p> <p>(b) international prognostic index (IPI) score (< 2 versus ≥ 2, The International Non-Hodgkin's Lymphoma Prognostic Factors Project (1993); Moskowitz (1999)).</p> <p>Eligible patients will be randomized into:</p> <p>Arm A: (tisagenlecleucel): Patients will receive lymphodepletion chemotherapy followed by infusion of tisagenlecleucel. Use of platinum-based bridging chemotherapy prior to lymphodepletion therapy is allowed.</p> <p>Arm B: (standard of care): Patients will receive platinum-based immunochemotherapy followed in responding patients with high dose chemotherapy and autologous hematopoietic stem cell transplantation (HSCT). High dose chemotherapy and autologous HSCT is not mandatory in these patients and they may continue therapy with SOC immunochemotherapy if deemed in the patient's best interest.</p> <p>Tumor and response assessments will be performed during the screening period (baseline within 2 weeks of randomization), six weeks after randomization (± 1 week), 12 weeks after randomization (± 1 week), 6 months after randomization (± 2 weeks), every 3 months thereafter (± 2 weeks) for the first year, every 6 months (± 4 weeks) for the second year, and annually thereafter (± 8 weeks) up to 5 years after randomization of the last patient.</p> <p>Cross-over to the other treatment arm, is allowed at any time after the Week 12 assessment after confirmed SD/PD by BIRC.</p>
Population	The study will randomize approximately 318 patients age 18 or greater.
Key Inclusion criteria	<ol style="list-style-type: none"> Histologically confirmed, aggressive B-cell NHL at relapse/progression after front line therapy. Aggressive B-cell NHL is heretofore defined by the following list of subtypes (Swerdlow et al 2016): <ol style="list-style-type: none"> DLBCL, NOS, FL grade 3B, Primary mediastinal B cell lymphoma (PMBCL), T cell rich/histiocyte rich large B cell lymphoma (T/HRBCL), DLBCL associated with chronic inflammation, Intravascular large B-cell lymphoma, ALK+ large B-cell lymphoma, B-cell lymphoma, unclassifiable, (with features intermediate between DLBCL and classical Hodgkin's Lymphoma (HL)), High grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements, High-grade B-cell lymphoma, NOS HHV8+ DLBCL, NOS DLBCL transforming from follicular lymphoma DLBCL transforming from marginal zone lymphoma DLBCL, leg type Relapse or progression within 365 days from last dose of rituximab and anthracycline containing first line immunochemotherapy or refractory (have not

	<p>achieved a CR or PR).</p> <p>3. Patient is considered eligible for autologous stem cell transplant (ASCT) as per local investigator assessment. Note: Intention to transplant and type of high dose chemotherapy (HDCT) regimen will be documented in the Interactive Response Technology (IRT) system and in the electronic Case Report Form (eCRF).</p> <p>4. Measurable disease:</p> <ul style="list-style-type: none"> a. Nodal lesions >15 mm in the long axis, regardless of the length of the short axis, and/or b. Extranodal lesions (outside lymph node or nodal mass, but including liver and spleen) >10 mm in long AND short axis <p>5. Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1</p> <p>6. Adequate organ function:</p> <p>Renal function defined as:</p> <ul style="list-style-type: none"> a. Serum creatinine of $\leq 1.5 \times$ upper limit of normal (ULN), OR estimated glomerular filtration rate (eGFR) ≥ 60 mL/min/1.73 m² <p>Hepatic function defined as:</p> <ul style="list-style-type: none"> b. Alanine Transaminase (ALT) and Aspartate Transaminase (AST) $\leq 5 \times$ ULN c. Bilirubin ≤ 2.0 mg/dL with the exception of patients with Gilbert syndrome who may be included if their total bilirubin is $\leq 3.0 \times$ ULN and direct bilirubin $\leq 1.5 \times$ ULN <p>Hematologic Function (regardless of transfusions) defined as:</p> <ul style="list-style-type: none"> d. Absolute neutrophil count (ANC) $> 1000/\text{mm}^3$ e. Absolute lymphocyte count (ALC) $> 300/\text{mm}^3$ and absolute number of CD3+ T cells $> 150/\text{mm}^3$ f. Platelets $\geq 50000/\text{mm}^3$ g. Hemoglobin > 8.0 g/dl <p>Adequate pulmonary function defined as:</p> <ul style="list-style-type: none"> h. No or mild dyspnea (\leq Grade 1) i. Oxygen saturation measured by pulse oximetry $> 91\%$ on room air j. Forced expiratory volume in 1 s (FEV1) $< 50\%$ and/or carbon monoxide diffusion test (DLCO) $< 50\%$ of predicted level <p>7. Must have a leukapheresis material of non-mobilized cells available for manufacturing. Note: Please refer to Section 6.2.2, Section 8.1 (Leukapheresis) for prohibited concomitant medications and washout times to ensure adequate collection as well as the [Investigational Leukapheresis, Cryopreservation and Scheduling Manual] for specific collection procedures.</p>
--	--

Key Exclusion criteria	<ol style="list-style-type: none"> 1. Prior treatment with anti-CD19 therapy or any prior gene therapy product 2. Patients with active central nervous system (CNS) involvement are excluded, except if the CNS involvement has been effectively treated (i.e. patient is asymptomatic) and local treatment was >4 weeks before randomization 3. Prior allogeneic HSCT 4. Uncontrolled acute life threatening infection 5. Any of the following cardiovascular conditions: <ul style="list-style-type: none"> • Unstable angina, myocardial infarction, coronary artery bypass graft (CABG), or stroke within 6 months prior to screening, • Left ventricle ejection fraction (LVEF) <45% as determined by echocardiogram (ECHO) or magnetic resonance angiography (MRA) or multigated acquisition (MUGA) within the past 12 months including the screening assessment. • New York Heart Association (NYHA) functional class III or IV (Chavey et al 2001), within the past 12 months. • Clinically significant cardiac arrhythmias (e.g., ventricular tachycardia), complete left bundle branch block, high-grade atrioventricular (AV) block (e.g., bifascicular block, Mobitz type II) and third degree AV block unless adequately controlled by pacemaker implantation. • Resting QTcF ≥450 msec (male) or ≥460 msec (female) at screening or inability to determine the QTcF interval • Risk factors for Torsades de Point (TdP), including uncorrected hypokalemia or hypomagnesemia, history of cardiac failure, or history of clinically significant/ symptomatic bradycardia, or any of the following: <ul style="list-style-type: none"> • Long QT syndrome, family history of idiopathic sudden death or congenital long QT syndrome • Concomitant medication(s) with a "Known Risk of Torsades de Point" per www.qtdrugs.org that cannot be discontinued or replaced by safe alternative medication. 6. Patients with active neurological autoimmune or inflammatory disorders (e.g., Guillain-Barré Syndrome (GBS), Amyotrophic Lateral Sclerosis (ALS))
Study treatment	<ul style="list-style-type: none"> • Arm A: A single dose of 0.6 to 6.0×10^8 of autologous tisagenlecleucel transduced T-cells administered via i.v. infusion after optional bridging chemotherapy and LD chemotherapy • Arm B: SOC with intent to transplant per local guidelines
Efficacy assessments	<ul style="list-style-type: none"> • Imaging (CT or MRI, PET-CT or PET), six weeks after randomization (\pm one week), 12 weeks after randomization (\pm one week), and every 3 months thereafter (\pm two weeks) for the first year, every 6 months (\pm four weeks) for the second year, and annually thereafter (\pm eight weeks) up to 5 years after randomization of the last patient, • physical examination, • bone marrow biopsy
Biomarker assessments	<ul style="list-style-type: none"> • Serum cytokine analysis • B-cell and T-cell levels • Immunophenotyping • Exploratory analysis on tumor biopsy
Pharmacokinetic assessments	<ul style="list-style-type: none"> • Cellular kinetics by flow cytometry (blood, bone marrow) • Cellular kinetics by qPCR (blood, bone marrow) • Immunogenicity (blood) <ul style="list-style-type: none"> • Rituximab pharmacokinetics (PK) by enzyme-linked immunosorbent assay (ELISA)

Key safety assessments	Adverse events (AEs and laboratory abnormalities (type, frequency and severity)). All patients treated with tisagenlecleucel will be monitored for specific toxicities for up to a total of 15 years following infusion, irrespective of their response to tisagenlecleucel. All patients will be monitored in this trial for 5 years after randomization, followed by semiannual and annual safety assessments in a separate long-term safety follow-up protocol (CCTL019A2205B) for an additional ten years.
Other assessments	<ul style="list-style-type: none"> Time to definitive deterioration in 36 item short form health survey (SF-36v2), Functional Assessment of Cancer Therapy Lymphoma (FACT-Lym), and EuroQol Visual Analogue Scale (EQ-VAS)
Data analysis	<p>Approximately 318 patients will be randomized in a 1:1 ratio to either tisagenlecleucel therapy or SOC therapy. During randomization, patients will be stratified by:</p> <ol style="list-style-type: none"> remission duration (refractory or relapsed <6 months v. 6 to 12 months) and international prognostic index score (IPI, <2 versus ≥2, (The International Non-Hodgkin's Lymphoma Prognostic Factors Project 1993; Moskowitz 1999). <p>Analyses data sets:</p> <ul style="list-style-type: none"> The Full Analysis Set (FAS) comprises all randomized patients. According to the intent to treat principle, patients will be analyzed according to the treatment and strata they have been assigned to during the randomization procedure. The Safety Set includes all patients who received at least one dose of any component of study treatment. Patients will be analyzed according randomized treatment. The PK analysis set consists of all patients who receive at least one dose of tisagenlecleucel and for whom at least one PK concentration value was available. <p>Statistical analysis: The primary endpoint is event free survival (EFS), defined as the time from the date of randomization to the date of the first documented disease progression or stable disease at or after the week 12 assessment by BIRC or death at any time. The week 12 assessment has a one week visit window, therefore the assessment can occur as early as week 11. Given this visit window, all responses of SD or PD after week 11 will be counted as an event. The primary efficacy objective is considered to be met if the null hypothesis, i.e. the survival functions for EFS in the two arms are identical, can be rejected based on a one-sided stratified weighted log-rank test at 2.5% level of significance. Distribution of EFS will be estimated using the Kaplan-Meier method. The median EFS along with 95% confidence intervals (CIs) will be presented by treatment group. The Cox regression model stratified by the randomization stratification factors will be used to estimate the hazard ratio (HR) of EFS, along with the 95% confidence interval. There will be no interim analysis for EFS. The analysis for EFS will be performed when at least 200 EFS events in the FAS have been documented by the BIRC.</p> <p>Sample size: The 9 month EFS rate is estimated to be 22.32% in SOC arm based on the ORCHAARD study and is assumed to be 40% in tisagenlecleucel arm. Due to delayed tisagenlecleucel infusion of 6 weeks and ignoring SD/PD at week 6, we assume piecewise hazard rate in both treatment arms. The hazard ratio between two arms during the first 6 weeks is assumed to be 1 and 0.61 after 6 weeks. Given those assumptions, a total of 200 EFS events are required to have 92% power at an one-sided 2.5% level of significance to reject the null hypothesis (i.e. the survival functions for EFS in the two arms are identical), using a stratified log rank test with equal weights.</p> <p>Considering a recruitment period of approximately 21 months using staggered enrollment rate of 2, 10, 16 patients in the first 3 months followed by 17 patients thereafter, and assuming 15% drop out rate, a total of approximately 318 patients will need to be randomized to the two treatment arms in a 1:1 ratio. Given the above assumptions, it is estimated that the 200th EFS event will be observed at approximately 23 months from the date of first patient randomized.</p> <p>Overall survival (OS) is a secondary endpoint and is defined as the time from date of randomization to date of death due to any cause, will also be compared between</p>

	<p>the two treatment arms. A maximum of two analyses are planned for OS: i) an interim analysis at the time of the primary analysis for EFS (provided EFS is significant) and ii) a final analysis approximately five years after randomization of the first patient if OS is not significant at the time of the primary analysis. The median OS along with 95% CIs will be presented by treatment group. OS will be compared between the two treatment groups using a weighted log-rank test stratified by randomization stratification factors.</p> <p>Safety: The assessment of safety will be based mainly on the incidence rates of AEs, their severity and seriousness, and laboratory assessments. Other safety data (e.g., physical assessments, electrocardiograms (ECGs), vital signs) will be summarized. For all safety analyses, the safety set will be used.</p> <p>Patient reported outcomes: Time to definitive deterioration for SF-36 v2 (physical and mental components), FACT-Lym (general score [G], lymphoma subscale [LymS], trial outcome index [TOI], total score [TS]), and EQ-VAS will be summarized using Kaplan-Meier methods. The estimated Kaplan-Meier plots will be provided and the unstratified log-rank test will be the primary method to compare the time to first deterioration between the two treatment groups. For SF-36 v2, a score decrease of 3 points or higher must be held to be considered “deteriorated”. For FACT-Lym, a score decrease of 3 points or higher in FACT-G, 2.9 points or higher in LymS, 5.5 points or higher in TOI, and 6.5 points or higher in TS must be held to be considered “deteriorated” For EQ-VAS, a score decrease of 7 points or higher must be held to be considered “deteriorated”.</p> <p>Summary statistics will be reported for each of items and scales over time by treatment arm. Repeated measures mixed-effects model will be carried to compare the two groups with respect to the change from baseline. Rates of improvement will be evaluated from baseline to each time point and will be compared between the two treatment groups using chi-square test. For the Euroqol 5 dimension (EQ-5D) health state profiles, the proportions of patients reported having “no”, “slight”, “moderate”, “severe”, or “extreme” problems at each time point will be reported.</p> <p>Cellular kinetics: Descriptive statistics will be summarized by month 3 response for all patients who receive tisagenlecleucel.</p> <p>Cellular kinetics in patients that receive tocilizumab for CRS management: For patients who received tocilizumab for cytokine release syndrome (CRS) management, the concentrations (transgene levels of tisagenlecleucel) will be summarized by time points, relative to time of tocilizumab dose. The cellular kinetic parameters will be presented with and without the use of tocilizumab.</p> <p>Rituximab levels: Rituximab PK will be to relate to the levels of B cells and to distinguish rituximab mediated aplasia vs. tisagenlecleucel mediated effects.</p>
Key words	Relapsed/refractory, NHL, tisagenlecleucel, CTL019

1 Introduction

1.1 Background

1.1.1 Overview of disease pathogenesis, epidemiology and current treatment

Non-Hodgkin Lymphomas (NHL) comprise a heterogeneous group of malignancies. Estimated new cases are 72,240 and deaths are 20,140 in the United States (US) for 2017 ([Siegel et al 2017](#)). In Europe, for 2012, there were an estimated 93,500 new cases and 37,800 deaths due to NHL ([Ferlay et al 2015](#)).

The 2008 World Health Organization (WHO) classification of hematopoietic and lymphoid tumors ([Jaffe 2009](#)), updated in 2016 ([Swerdlow et al 2016](#)), represents the established guidelines for the diagnosis of malignant lymphomas. The classification is based on the recognition of distinct diseases according to a combination of morphology, immunophenotype, genetic, molecular, and clinical features. Lymphoid neoplasms are stratified according to cell lineage and derivation from precursor or mature lymphoid cells into: immature lymphoid neoplasms, mature B-cell neoplasms, T-cell and natural killer (NK)-cell neoplasms, and post-transplant lymphoproliferative disorders (PTLD). Mature B-cell lymphomas are further classified into indolent lymphomas (e.g. multiple myeloma, follicular lymphoma – except for FL3B that is considered as an aggressive subtype-) and aggressive lymphomas (e.g. diffuse large B-cell lymphoma [DLBCL], Burkitt lymphoma, primary mediastinal B cell lymphoma [PMBCL], T cell rich/histiocyte rich large B cell lymphoma [THCBCL], DLBCL associated with chronic inflammation, intravascular large B-cell lymphoma, ALK+ large B-cell lymphoma). DLBCL is the most frequent lymphoma subtype, representing 30-40% of all NHLs for western countries ([Chiappella et al 2016](#), [Al-Hamadani et al 2015](#)). Estimated incidence in the European Union is 3.8/100,000/year, increasing with age (reaching a maximum after 75 years) and with considerable variation across European countries ([Sant et al 2010](#), [Tilly et al 2015](#)). For the US, the incidence for the 2002-2011 period of was 6.9/100,000/year; also increasing with age (32.7/100,000/year after 65 years) ([Howlader et al 2011](#)).

The prognosis of patients with DLBCL and other B-cell aggressive lymphomas depends on individual risk factors. The International Prognostic Index (IPI) for aggressive NHL includes five risk factors independently prognostic of overall survival (OS) ([The International Non-Hodgkin's Lymphoma Prognostic Factors Project 1993](#)):

- Patient age (≤ 60 years vs. > 60 years)
- Serum lactate dehydrogenase (LDH) (normal $\leq 1 \times \text{ULN}$ vs. elevated $> 1 \times \text{ULN}$)
- ECOG performance status (0 or 1 vs. ≥ 2)
- Stage (stage I or stage II vs. stage III or stage IV)
- Extranodal site involvement (0 or 1 vs. 2–4)

Patients with ≥ 2 risk factors after age-adjustment have a poor prognosis with a 5 year OS rate of 21-46%. Age- and stage-adjusted modifications from diagnosis are used for younger

patients with localized disease ([Moller et al 2003](#)). Very recently a revised IPI, the National Comprehensive Cancer Network International Prognostic Index (NCCN-IPI), has been proposed to better reflect the individual patient's risk in the rituximab era ([Zhou et al 2014](#)). Very similar to the original IPI, five prognostic factors were identified:

- Patient age (>40 to ≤60 vs. >60 to ≤75 vs. >75 years)
- Normalized serum LDH (>1 to ≤3 vs. >3 x ULN)
- ECOG performance status (0 or 1 vs. 2–4)
- Ann Arbor Stage (stage I or stage II vs. stage III or stage IV)
- Extranodal site involvement, that is, disease in bone marrow, CNS, liver/gastrointestinal (GI) tract, or lung (yes vs. no)

The NCCN-IPI can discriminate four prognostic groups: low (0-1), low-intermediate (2-3), high-intermediate (4-5), and high (6-8).

DLBCL is a heterogeneous disease with several molecular subtypes based on gene expression profiling (GEP) and based on biologic similarity to normal stages of B-cell development classified into: i) germinal center-B-cell-like (GCB; CD10+, or BCL6+, IRF4/MUM1-), ii) activated B-cell-like (ABC), iii) primary mediastinal large B cell lymphoma (PMBCL) and iv) type 3 (unclassifiable) DLBCL ([Swerdlow et al 2016](#), [Lenz et al 2008](#), [Alizadeh et al 2000](#)). The GCB and ABC subtypes arise from B-cells at different stages of differentiation (GCB originates from germinal center B-cells, whereas ABC arises from post-germinal-center B-cells transitioning into plasma cells) and differ in their clinical outcome. GEP is not routinely used, however, immunohistochemistry (IHC)-based algorithms predict a 5-year OS of 76% in GCB tumors compared to 34% in ABC tumors ([Hans et al 2004](#)). Indeed, inferior survival for ABC DLBCLs was also observed in patients treated with rituximab and CHOP chemotherapy ([Lenz et al 2008](#)).

Frontline treatment of patients with newly diagnosed DLBCL and other B-cell aggressive NHL is generally tailored based on age, age-adjusted IPI and feasibility of dose intensified approaches ([Tilly et al 2015](#)). The combination of rituximab (anti-CD20) with anthracycline-based chemotherapy (e.g., cyclophosphamide, doxorubicin, vincristine and prednisone [R-CHOP]) given every 21 days represents the standard frontline treatment for most patients with DLBCL. Despite most patients being cured with conventional frontline immunochemotherapy, around one-third will not respond (i.e., will not achieve a CR or PR) or will relapse or progress after treatment. More than half of all these treatment failures include non-responding and relapsing patients within a year after the standard frontline immunotherapy (early relapsed). These patients have a poor prognosis, particularly those who do not respond to second-line chemotherapy ([Sarkozy and Coiffier 2015](#), [Coiffier et al 2016](#), [Friedberg 2011](#), [Elstrom et al 2010](#)). Patients who achieve at least a partial response to second-line therapy have a 35-50% chance of long-term survival, whereas those with stable or progressive disease exhibit less favorable outcomes with a median OS of around 3.5 months ([Elstrom et al 2010](#), [van den Neste et al 2016](#)), similar to the expected survival of approximately 4 months for patients left untreated ([Elstrom et al 2010](#), [van den Neste et al 2016](#)).

For patients with r/r DLBCL and other aggressive B-cell lymphomas with adequate performance status (defined by age and absence of major organ dysfunctions), the European Society for Medical Oncology (ESMO) and NCCN clinical treatment guidelines recommend a

salvage regimen with rituximab (R) and platinum-based chemotherapy, followed in **responsive** patients by high-dose chemotherapy and autologous HSCT (Tilly et al 2015, NCCN v7 2018). The most frequently used salvage regimens for these patients include R-DHAP (R-dexamethasone, cytarabine, cisplatin), R-ICE (R-ifosfamide, carboplatin, etoposide) or R-GDP (R-cisplatin, gemcitabine, dexamethasone) (Tilly et al 2015, NCCN v7 2018). Response rates to these conventional salvage immunochemotherapies is over 60%, including about 30% of complete responses (Coiffier et al 2016). Patients refractory or relapsing within 12 months of first-line therapy have a particularly poor prognosis even with autologous HSCT (Gisselbrecht et al 2010). Without autologous HSCT, chemotherapy provides only short-term disease control in these patients (Elstrom et al 2010).

Three studies are relevant to underline the medical need in patients failing first-line treatment (Table 1-1).

Table 1-1 Phase III trials in relapsed/refractory DLBCL

Trial (N randomized)	CORAL (n=400) ^{3,4}		LY.12 (n=619) ²		ORCHARRD (n=447) ¹	
Treatment Arm	ICE	DHAP	GDP	DHAP	R-DHAP	O-DHAP
N treated	197	191	303	302	223	222
	%	%	%	%	%	%
ORR in patients who received at least one cycle of salvage therapy regardless of time to relapse/resistance status						
CR + PR	63.5	62.8	46.2	44.7	42.2	37.8
SD	11.7	11.5	5.6	6.0	29.6	28.8
PD	19.3	18.3	25.7	28.8	15.2	17.6
UNK	5.1	7.3	22.5	20.5	13.0	15.8
Completed induction phase with CR/PR/SD	74.7		51.2		69.2	
Patients receiving ASCT, % of all treated	51.3	55	52.1	49.3	37.2	33
Outcome in Refractory and Relapsed within 12 months (early relapsed) from last therapy						
ORR, % in CR/PR (% in R > 12 mo)	46.5 (v. 88%)		35.3 (v. 70%)		29 (v. 67%)	
PFS, %*	23 [£] (% not reported in R>12 mo)		NA		20 (v. 50% in R > 12 mo; HR 0.32, p<0.0001) [#]	
EFS, %*	20 ^{££} (v. 45% in R > 12 mo; p<0.001)		NA		NA	
OS, %*	39 ^{££} (v. 64% in R>12 mo, p<0.001)		NA		30 (v. 60% in R>12mo; HR 0.40, p<.0001) ^{##}	
Outcome in Refractory and Relapsed within12 months from last therapy with ASCT (vs no ASCT)						
PFS, %* / mPFS, mo (vs no ASCT)*	39 / 18.7 (v. 14 / 2.8) [£]		NA		NA / 11.6 (v. NA / 1.4) ^{###}	
OS, %* / mOS, mo (vs no ASCT)*	NA		NA		NA / Not Reached (v. NA / 7.1) ^{###}	
NA: not available; R>12: relapsed after 12 months of front line * % of time related parameters by study presented at 3y for CORAL, 2y for ORCHARRD and 4y for LY. 12; £ Data for the 187 patients in CORAL study who received prior rituximab ££ Data for all the patients in CORAL regardless of prior rituximab (n=228 refractory/early relapsed and 160 with late relapse) # median PFS (by BIRC, all pts regardless of arm): refractory/relapsed <12m: 1.5 mo vs R>12: 23.8 mo (Novartis unpublished internal data) ## median OS (all pts regardless of arm): refractory/relapsed <12m: 10.0 mo vs R>12: not reached (Novartis unpublished internal data) ### ASCT: performed in 25.6% of r/r <12m vs 58.9% in R>12 (Novartis unpublished internal data)						
¹ van Imhoff et al (2017). ² Crump et al (2014), ³ Gisselbrecht et al (2010), ⁴ van den Neste et al (2016).						

The ‘Collaborative Trial in Relapsed Aggressive Lymphoma’ (CORAL) study demonstrated that approximately 60% of patients with r/r DLBCL respond to second-line salvage immunochemotherapy (R-ICE or R-DHAP), and around 50% of patients receiving this salvage therapy can further receive ASCT (Gisselbrecht et al 2010) (Table 1-1). Data from this trial also shown that patients refractory or relapsing within 12 months of rituximab-containing first-line therapy had a particularly poor prognosis, with only 14% of patients not

undergoing autologous HSCT being event free at 3 years (median progression free survival (mPFS)) in these patients only 2.8 months). On the other hand, for refractory or early relapsing patients undergoing autologous HSCT, the 3-year PFS rate was 39% (and median PFS 18.7 months), highlighting the importance of autologous HSCT as treatment option in this patient population. Response rate was also lower in patients who were refractory or relapsing within 12 months of front line therapy (46.5% vs 87.5% in patients relapsing after 12 months of front line therapy). Another important finding from this trial is that patients not undergoing autologous HSCT can still be rescued and eventually transplanted with further chemotherapy (Gisselbrecht et al 2010, van den Neste et al 2016), data not shown in Table 1-1. Interestingly, 39% of patients not undergoing transplant after first salvage therapy (i.e., R-ICE or R-DHAP) responded after a second salvage therapy. Indeed, 31% of all patients receiving second salvage were eventually transplanted (87.5% auto / 12.5% allo) and 88% of these transplanted patients were alive at 1 year (median OS not reached at the time of the analysis). On the other hand, patients with SD or PD after initial salvage therapy not responding to second salvage therapy have a dismal prognosis, with a median OS of only 3.4 months (van den Neste et al (2016), data not shown in Table 1-1) which highlights the need of developing new therapies for these patients.

The National Cancer Institute of Canada Clinical Trials Group (NCIC-CTG) LY.12 trial compared the efficacy GDP versus DHAP and subsequent consolidation by high dose chemotherapy/autologous HSCT in 619 patients with relapsed/refractory aggressive NHL (DLBCL, peripheral T-cell lymphoma, and anaplastic large cell lymphoma were enrolled in this trial) (Crump et al 2014). As observed in CORAL trial, response rate was lower in patients who were refractory or had relapsed within 12 months from initial therapy (35.3% vs 70% in patients relapsing after 12 months of front line therapy) (Table 1-1). Outcome in patients refractory and relapsed within 12 months from last therapy according to ASCT are not available for this trial.

The short term nature of disease control in many patients with r/r DLBCL and poor prognosis of early relapses was also confirmed in the ORCHARRD trial, which compared the anti-CD20 directed antibody ofatumumab (O) plus DHAP versus rituximab (R) plus DHAP followed by autologous HSCT in patients with r/r DLBCL after first-line treatment (van Imhoff et al 2017). All patients enrolled in this trial were refractory to or had relapsed following first-line treatment with rituximab and an anthracycline-based chemotherapy regimen and therefore, this study might represent the most relevant efficacy data of salvage therapy in the rituximab era. Of the 447 randomized patients, 71% were refractory or early relapsed (i.e., did not achieve CR, progressed or experience response for < 12 months) after front line R-CHOP. As was seen in CORAL and LY.12 trials, these patients with refractory or early relapsed disease had a worse outcome when compared with patients relapsing after 12 months of initial therapy [ORR: 29% vs 67%, 2-year PFS: 20% vs 50% (HR 0.32, p<0.0001) and 2-year OS: 30% vs 60% (HR 0.40, p<.0001)]. As expected, median PFS and OS values were also significantly higher in patients with late relapse (1.5 vs 23.8 months for PFS and 10.0 vs not reached for OS in refractory/early relapsed vs late relapsed patients). ASCT in this group of patients also increased the median PFS and OS when compared with the patients not able to be transplanted (median PFS in transplanted 11.6 months vs 1.4 months in non-transplanted; median OS in transplanted not reached vs 7.1 months in non-transplanted patients) (Table 1-1).

These data confirm the poor prognosis of refractory and early relapsing patients after front line therapy and the unmet need for this patient population.

Recently, the SCHOLAR-1 meta-analysis (n=636) has reported on the very poor outcome of patients with DLBCL refractory to anti-CD20 monoclonal antibody- and anthracycline-containing regimens (Crump et al 2017). In this meta-analysis, both the ORR and the OS were quite similar regardless of the number of prior lines and the refractory group (refractory after 1 line vs \geq nd line vs relapse within 1 year of autologous HSCT): i) for ORR: 20 vs 26 vs 34%; ii) for median OS: 7.1 vs 6.1 vs 6.2 months. The authors concluded that patients with chemorefractory DLBCL have homogeneous and consistently poor outcomes, regardless of refractory subgroup and line of therapy.

Concerning r/r FL3B and other aggressive B-cell lymphomas, these patients are also treated according to the DLBCL treatment algorithm and in particular the FL3B subtype is regarded as aggressive lymphoma, with a clinical behaviour very similar to DLBCL and with frequent histological transformation into DLBCL (Dreyling et al 2016, NCCN v13 2017). Indeed, this aggressive FL3B subtype is generally excluded from clinical trials exploring new therapies (e.g., obinutuzumab, idelalisib) for indolent NHL (Sehn et al 2015, Sehn et al 2016, Gopal et al 2014).

In summary, after failure of rituximab containing first line therapy several chemotherapy salvage options are available but none of them seems to be superior from the others. Although all current treatment options have not been compared in a randomized setting, the observed results are quite consistent regardless of the line of therapy and particularly poor in the group of patients with refractory disease and early relapse (i.e., within 12 months of last therapy). This is as well supported by the recent SCHOLAR-1 meta-analysis, showing that the DLBCL population has homogeneous and consistently poor outcomes regardless of refractory group, line of therapy and disease stage (Crump et al 2017).

In conclusion, refractory and early relapsed aggressive B-cell NHL represents a significant unmet medical need and thus novel therapies are urgently needed for this patient population.

1.1.2 Overview of tisagenlecleucel

Adoptive T-cell therapy for cancer involves the infusion of native or genetically modified mature T cells that have the capacity to recognize and possibly eliminate the patient's malignant cells. In particular, chimeric antigen receptor (CAR)-based approach involves engineering T cells with sequences that encode antibody-based antigen recognition moieties linked to signaling domains. CAR-T cells specifically target and destroy tumor cells in a Major Histocompatibility Complex (MHC) independent manner (Mellman et al 2011).

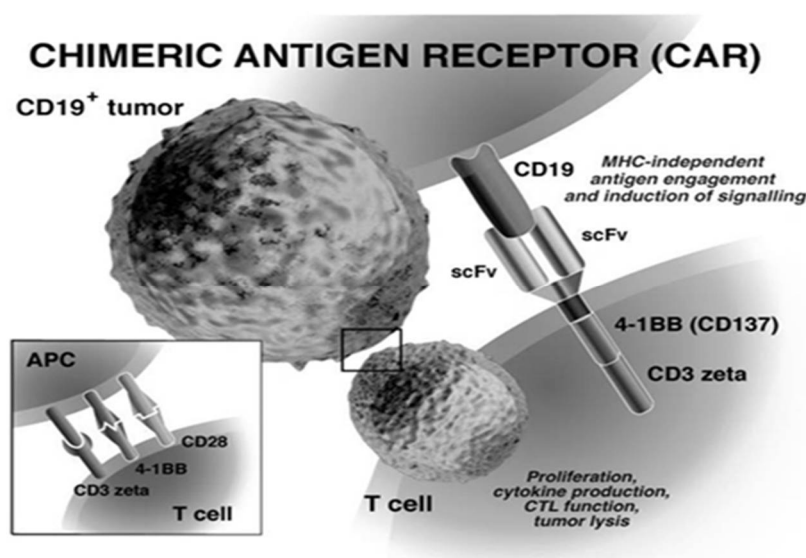
A promising target antigen for B cell malignancies is CD19, a cell-surface protein whose expression is restricted to B cells and their precursors (Sadelain et al 2003, Porter et al 2011), with no expression on hematopoietic stem cells or non-B cell tissues. CAR-T cells targeting CD19 have been developed to target B cell malignancies.

First generation CARs contain the T-cell receptor (TCR) activation signal domain consisting of TCR ζ . Second generation CARs contain costimulatory signaling domains as well: either CD28 or 4-1BB. The 3rd generation CARs contain further advancements such as double

costimulatory modules comprised of CD28, 4-1BB plus TCR ζ (June 2007, June et al 2009, Kohn et al 2011).

Tisagenlecleucel (CART-19) is a second generation CAR-T cell that uses the autologous peripheral blood T cells that have been genetically modified *ex vivo* to target CD19 on the surface of B cells. As shown in Figure 1-1, the CAR approach uses genetically programmed lymphocytes transfected with chimeric receptor genes to combine the effector functions of T lymphocytes with the ability of antibodies to recognize predefined surface antigens with high specificity in a non-MHC restricted manner (Gross et al 1989, Pinthus et al 2003). These receptors have the ability to recognize intact membrane proteins independent of antigen processing. The tumor antigen binding function of CAR is usually accomplished by the inclusion of a single chain variable fragment (scFv) antibody, containing the heavy chain variable domain (V_H) and light chain variable domain (V_L) joined by a peptide linker of about 15 residues in length (Mullaney and Pallavicini 2001).

Figure 1-1 Tisagenlecleucel chimeric antigen receptor design



Recent clinical trials of tisagenlecleucel in r/r CLL, r/r ALL, and r/r B-cell lymphomas have shown promising and durable anti-tumor efficacy (Porter et al 2011, Grupp et al 2013, Maude et al 2014, Schuster et al 2017). Consequently, tisagenlecleucel appears to be a therapeutic alternative for patients with B cell malignancies (including DLBCL) refractory to the current therapies. For further information refer to the [Tisagenlecleucel Investigator's Brochure].

1.1.2.1 Non-clinical experience

Extensive literature supports the use of engineered T cells for tumor immunotherapy in rodent tumor models (Calogero et al 2000, Clay et al 2002, Hombach et al 2002, Pule et al 2003, Sadelain 2003). The incorporation of costimulatory signaling modules such as CD28 and 4-1BB in second generation CARs increases potency of the engineered T cells in pre-clinical studies (Finney et al 1998, Krause et al 1998, Eshhar et al 2001, Maher et al 2002, Finney et al 2004, Friedmann-Morvinski et al 2005, Brentjens et al 2010). The pre-clinical

data supporting CAR T-cell persistence, expansion and anti-tumor efficacy have been published ([Gross and Eshhar 1992](#), [Milone et al 2009](#)).

1.1.2.2 Clinical experience

There are currently 12 ongoing therapeutic studies of tisagenlecleucel. A summary of ongoing and completed clinical trials can be found in the [Tisagenlecleucel Investigator's Brochure].

1.1.2.2.1 Efficacy and safety of tisagenlecleucel in aggressive NHL

Two clinical trials with tisagenlecleucel in DLBCL patients failing or not being candidates to HSCT are ongoing:

CTL019A2101J (NCT02030834) ([Schuster et al 2017](#)): this is a single-arm, single-institution trial ongoing at University of Pennsylvania. Patients with CD19+ DLBCL or FL with no curative treatment options, who relapsed, or had residual disease after ASCT, or were not eligible for autologous or allogeneic HSCT, are eligible for the trial. Patients had to have partial response or stable disease to most recent therapy. The 6-month ORR in DLBCL patients was 50% (7/14 patients), with CR achieved in 6 patients (43%; 95% CI: 18-71%). Sustained remissions were achieved, and at a median follow-up of 28.6 months, 86% of patients with DLBCL who had a response (95% CI, 33 to 98) had maintained the response. Cytokine-release syndrome (CRS) was observed in 57% of patients overall, including 18% (n=5 patients) with grade ≥ 3 (both DLBCL and FL taken together). One CR patient with severe CRS required tocilizumab leading to rapid reversal of symptoms. No patient received glucocorticoids and no deaths from CRS were observed in this study. Eleven patients (39%) had neurologic toxic effects related to tisagenlecleucel therapy. Effects ranged from mild cognitive disturbance to global encephalopathy (grade 3 or higher); three patients (11%) had encephalopathy of grade 3 or higher. The neurologic symptoms were self-limiting and resolved fully within 1 week in all but one patient. One patient with follicular lymphoma who had encephalopathy had progressive neurologic deterioration that resulted in death. This patient had a history of optic atrophy and was the only patient who underwent fludarabine-based lymphodepletion.

CTL019C2201 (NCT02445248) (**JULIET trial**) ([Schuster et al 2017](#)): this is a Novartis sponsored ongoing single-arm, multicenter trial. As of 8-Mar-2017 cut off, 99 pts received a single dose of tisagenlecleucel. Median time from infusion to data cut-off was 3.7 mo. Median age was 56 years (range, 22-76). Fifty percent of the patients received at least 3 prior lines of therapy, including 47% prior ASCT. Primary efficacy analysis based on 81 patients showed clinically meaningful and durable responses including 53% overall response rate (ORR) (40% CR) which were sustained at 6 months (ORR 37%, 30% CR). Median duration of response (DOR) and OS were not reached and most patients achieving CR at month 3 have remained in CR at data cut-off. Safety profile of tisagenlecleucel in r/r DLBCL patients is well characterized and manageable, consistent with previous tisagenlecleucel experience. Any grade CRS was experienced by 58% of patients (15% grade 3; 8% Grade 4).

[Section 4.6](#) outlines expected and potential toxicities related to tisagenlecleucel, most of which occur within 8 weeks of infusion.

For further information refer to the [Tisagenlecleucel Investigator's Brochure].

1.1.2.2.2 Cellular kinetics

In adult r/r DLBCL patients from Study C2201, tisagenlecleucel typically exhibit an initial rapid expansion phase, achieving maximal expansion around Day 9 (D9) followed by a bi-exponential decline. The persistence of tisagenlecleucel transgene in peripheral blood has been observed for up to 18 months (data not published yet). All responding patients demonstrated expansion of transgene levels. No clinically relevant impact of patient characteristics and prior therapy on expansion were observed. Moreover, cellular and humoral immunogenicity had no impact on the cellular kinetics or clinical outcome ([Awasthi et al 2017](#)).

In study A2101J, median peak tisagenlecleucel expansion in blood occurred at 8 and 10 days after infusion in responders and non-responders, respectively. No difference was noted between peak CD8-tisagenlecleucel and peak CD4-tisagenlecleucel expansion in responders and non-responders. Among 16 patients in CR (including both DLBCL and FL), 14 had consistently detectable tisagenlecleucel DNA at 6 to 24 months post tisagenlecleucel infusion. Two DLBCL patients lost detectable tisagenlecleucel DNA, one at 3 months and one at 4 months, yet both continue in complete response at 23 and 29 months, respectively.

1.2 Purpose

Despite that most patients with aggressive B-cell NHL, can be cured with conventional frontline immunochemotherapy (e.g., R-CHOP), around one-third of patients will not respond (i.e., will not achieve a CR or PR) or will relapse or progress after front-line treatment. More than half of all these treatment failures include patients not responding (refractory) or relapsing/progressing within a year after the standard frontline immunotherapy (defined as “early relapses”). These patients have a poor prognosis, particularly if they do not respond to further salvage immunochemotherapy or are not eligible for HSCT ([Sarkozy et al 2015](#), [Coiffier et al 2016](#), [Friedberg 2011](#), [Elstrom et al 2010](#)). Novel therapies for refractory and early relapsed DLBCL patients are thus urgently needed.

Given the activity of tisagenlecleucel in DLBCL patients after two or more prior therapies, this phase III trial aims at providing randomized assessment of the safety and efficacy of the treatment strategy with this novel agent against the current standard of care treatment strategy, with the potential to provide additional treatment options for this patient population.

2 Objectives and endpoints

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary Objective(s)	
To compare tisagenlecleucel treatment strategy to SOC treatment strategy therapy with respect to delaying the composite event of disease progression / stable disease at or after the week 12 assessment; or death at any time.	<ul style="list-style-type: none"> EFS, defined as time from date of randomization to the date of first documented disease progression or stable disease at or after the week 12 (± 1 week) assessment, as assessed by blinded independent review committee (BIRC) per Lugano criteria, or death at any time
Secondary Objective(s)	
<ul style="list-style-type: none"> To compare tisagenlecleucel treatment strategy to SOC treatment strategy with respect to EFS as assessed by local investigator. 	<ul style="list-style-type: none"> EFS as assessed by local investigator
<ul style="list-style-type: none"> To compare tisagenlecleucel treatment strategy to SOC treatment strategy with respect to overall survival (OS). 	<ul style="list-style-type: none"> OS: defined as the time from randomization to date of death
<ul style="list-style-type: none"> To compare tisagenlecleucel treatment strategy to SOC treatment strategy with respect to overall response rate (ORR) To evaluate duration of response (DOR) by BIRC and local investigator. 	<p>The following endpoints will be evaluated by BIRC and investigator assessment per Lugano criteria:</p> <ul style="list-style-type: none"> ORR: overall response rate as per the Lugano criteria Duration of response: time from the date of first documented response of CR or PR to the date of first documented progression (SD or PD at or after the week 12 (± 1w) assessment will be considered progression) or death due to aggressive B-cell NHL
<ul style="list-style-type: none"> To evaluate safety of tisagenlecleucel treatment strategy versus SOC treatment strategy 	<ul style="list-style-type: none"> Type, frequency and severity of serious and non-serious adverse events and laboratory abnormalities and discontinuations due to adverse events
<ul style="list-style-type: none"> To compare patient reported outcomes (PRO) of health-related quality of life (HRQoL) in both treatment arms. 	<ul style="list-style-type: none"> Time to definitive deterioration in SF-36v2, FACT-Lym, and EQ-VAS
<ul style="list-style-type: none"> Evaluate efficacy and safety of both treatment arms in histological subgroups (DLBCL, NOS, FL3B, other) and molecular subgroups (e.g., GCB, ABC, other) 	<ul style="list-style-type: none"> EFS, OS and AE
<ul style="list-style-type: none"> To characterize the in vivo cellular kinetics of tisagenlecleucel transduced cells into target tissues (blood, bone marrow, cerebral spinal fluid and other tissues if available), as measured by qPCR summarized by clinical response 	<ul style="list-style-type: none"> Summary of qPCR detected tisagenlecleucel transgene concentrations in peripheral blood and bone marrow (and other tissue, if available), and cellular kinetic parameters from peripheral blood profile samples by time point and clinical response status
<ul style="list-style-type: none"> To characterize the incidence and prevalence of tisagenlecleucel immunogenicity (humoral and cellular) 	<ul style="list-style-type: none"> Summary of pre-existing and treatment induced immunogenicity (cellular and humoral) of tisagenlecleucel

Objective(s)	Endpoint(s)
<ul style="list-style-type: none"> To characterize the impact of pre-existing and treatment induced immunogenicity (cellular and humoral) on cellular kinetics and efficacy 	<ul style="list-style-type: none"> Levels of pre-existing and treatment induced immunogenicity. Cellular kinetic parameters, concentration-time profile by immunogenicity category (positive/negative), and efficacy (Month 3 response)
<ul style="list-style-type: none"> To assess presence of RCL in patients receiving tisagenlecleucel 	<ul style="list-style-type: none"> RCL by VSV-qPCR
Exploratory Objective(s)	
<ul style="list-style-type: none"> Characterize the in vivo cellular kinetics (levels, expansion, persistence) of tisagenlecleucel transduced cells in peripheral blood and to target tissues if available as measured from flow cytometry data, for randomized patients who receive tisagenlecleucel therapy 	<ul style="list-style-type: none"> Cellular kinetics parameters, as summarized by clinical response: C_{max}, T_{max}, AUCs, C_{last}, T_{last}, and/or other relevant parameters in peripheral blood, bone marrow as appropriate
<ul style="list-style-type: none"> Characterize immunogenicity including pre- and post-for Arm B 	<ul style="list-style-type: none"> Incidence and prevalence of immunogenicity (cellular and humoral)
<ul style="list-style-type: none"> Characterize and summarize cellular kinetics by use of tocilizumab and also by CRS grade for patients receiving tisagenlecleucel therapy 	<ul style="list-style-type: none"> C_{max}, T_{max}, AUCs, and other cellular kinetic parameters, use of tocilizumab (YES/NO), and CRS grade
<ul style="list-style-type: none"> To explore the relationship between tisagenlecleucel cellular kinetics, dose, and clinical response for randomized patients who receive tisagenlecleucel therapy 	<ul style="list-style-type: none"> parameters: C_{max}, T_{max}, AUCs, others as appropriate and clinical response parameters (e.g. ORR, DOR, dose)
<ul style="list-style-type: none"> Summarize rituximab PK and explore the relationship between rituximab PK, B-cells and clinical response for randomized patients who receive tisagenlecleucel therapy 	<ul style="list-style-type: none"> Summary of rituximab concentrations (pre-/post- tisagenlecleucel infusion) with ORR, DOR, PFS, and B cell levels
<ul style="list-style-type: none"> Explore relationship in baseline tumor biopsy specimens between CD19, PD1 and PD-L1 expression, and clinical response in Arm A 	<ul style="list-style-type: none"> ORR, DOR, PFS, CD19 expression, PD-1, PD-L1 expression
<ul style="list-style-type: none"> Profile blood soluble markers (e.g. IL-6, gamma interferon) and their correlation with safety and efficacy in Arm A 	<ul style="list-style-type: none"> ORR, DOR, PFS, EFS and OS, Concentrations of soluble factors in blood, CRS grade and neuronal toxicity
<ul style="list-style-type: none"> Characterize B cell levels over time and relationship with transgene persistence, clinical response 	<ul style="list-style-type: none"> B cell levels, cellular kinetics, and clinical response
<ul style="list-style-type: none"> Describe the composition of T-cell subsets (immunophenotyping in peripheral blood), summarized by clinical response in Arm A 	<ul style="list-style-type: none"> ORR, DOR, PFS, EFS and OS, CTL019-positive/CD3-positive/ CD4-positive and CTL019-positive/CD3-positive/CD8-positive T cells and other leukocyte subsets
<ul style="list-style-type: none"> Tisagenlecleucel efficacy in double-hit/triple hit lymphoma patients (Bcl-2, bcl-6 and c-myc expression) 	<ul style="list-style-type: none"> ORR, DOR, PFS, EFS and OS
<ul style="list-style-type: none"> To assess health care resource utilization (HCRU) with respect to hospitalization (i.e. length of stay, frequency), outpatient visit (i.e. frequency), and concomitant medication use for selected adverse events (eg, CRS and Neurological events) 	<ul style="list-style-type: none"> HCRU with respect to hospitalization, outpatient visits, and concomitant medication use for selected adverse events

3 Study design

This is a randomized, open label, multicenter phase III trial comparing the efficacy, safety, and tolerability of tisagenlecleucel treatment strategy to SOC treatment strategy in adult patients with aggressive B-cell NHL after failure of rituximab and anthracycline containing

first line immunochemotherapy. Failure of frontline therapy is defined as refractoriness (lack of response or progression during therapy) or relapse/progression within 365 days of last dose of first line therapy (in patients who achieved CR or PR on first line therapy).

All screened patients will undergo non-mobilized leukapheresis for autologous T cell collection after obtaining informed consent. During the screening period, no lymphoma-specific therapy is allowed prior to randomization. During randomization, patients will be stratified by:

- (a) remission duration (refractory or relapsed < 6 months from last dose of first line therapy vs. 6 - 12 months inclusive) and
- (b) international prognostic index (IPI) score (<2 versus ≥ 2 , [The International Non-Hodgkin's Lymphoma Prognostic Factors Project \(1993\)](#), [Moskowitz 1999](#)).

Eligible patients will be randomized into:

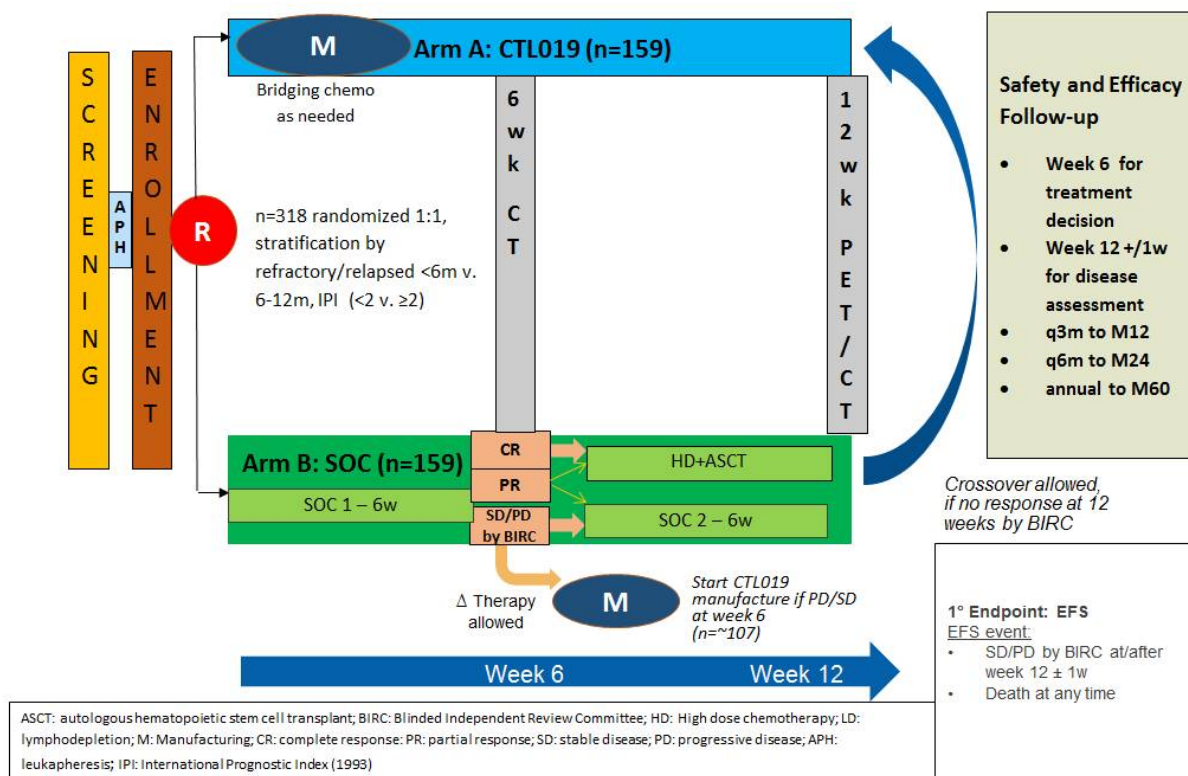
Arm A: (tisagenlecleucel treatment strategy, CTL019 after optional bridging chemotherapy and LD chemotherapy): Patients will receive lymphodepletion chemotherapy followed by infusion of tisagenlecleucel. Use of platinum-based bridging chemotherapy (recommended regimens include R-ICE, R-GDP, R-DHAP, or R-GemOx, and can be adjusted as per local practice, see [Section 6.1.1](#)) after randomization and prior to starting lymphodepletion therapy is allowed. In order to comply with the 4 week washout period for rituximab therapy, prior to CTL019 infusion (see [Section 6.2.2](#)), rituximab may need to be omitted from the last cycle of bridging chemotherapy.

Arm B: (standard of care treatment strategy, standard of care chemotherapy with transplant): Patients will receive platinum-based immunochemotherapy followed in responding patients with high dose chemotherapy and autologous hematopoietic stem cell transplantation (HSCT). Cells collected as part of the leukapheresis procedure during cannot be used for stem cell transplant. A separate collection of cells will be needed if patient is to proceed to autologous HSCT. High dose chemotherapy (HDCT) and autologous HSCT is not mandatory in responding patients and they may continue therapy with SOC immunochemotherapy rather than proceeding to HDCT + autologous HSCT if deemed in the patient's best interest by the treating physician. After receiving 6 weeks of platinum-based immunochemotherapy non-responding patients (SD or PD), may change therapy to one of the other recommended treatments, ibrutinib, or lenalidomide. If the assessment of SD or PD is confirmed by BIRC, the investigator may request manufacturing of tisagenlecleucel. In case of suboptimal response in responding patients, a change in therapy to one of the other recommended treatments is allowed. After receiving 12 weeks of SOC therapy, patients with PR FDG+ disease per local assessment may request manufacturing of tisagenlecleucel. Rules for crossover at the Week 12 (± 1 week) visit are detailed in [Section 8.3.3](#).

Tumor and response assessments will be performed during the screening period (baseline within 2 weeks of randomization), six weeks after randomization (\pm one week), 12 weeks after randomization (\pm one week), 6 months after randomization (\pm two weeks), every 3 months thereafter (\pm two weeks) for the first year, every 6 months (\pm four weeks) for the second year, and annually thereafter (\pm eight weeks) up to 5 years after randomization of the last patient. All patients who have disease progression determined by the local investigator at

any time per Lugano classification 2014 require an expedited central tumor response review by the BIRC.

Figure 3-1 Study design



4 Rationale

4.1 Rationale for study design

This is a randomized, open label, multicenter phase III trial to determine the efficacy and safety of tisagenlecleucel treatment strategy in adult patients with relapsed or refractory aggressive B-cell NHL after failure of rituximab and anthracycline containing frontline immunochemotherapy.

The outcome of patients with refractory/early relapsed DLBCL treated with first salvage therapy is poor, in particularly for those who do not respond to the salvage therapy, who have a median life expectancy of only 4 months (Elstrom et al 2010, van den Neste et al 2016, Friedberg 2011). As was shown by the SCHOLAR-1 meta-analysis (Crump et al 2016) patients with chemorefractory DLBCL have consistently poor outcomes, regardless of line of therapy, with a median survival of approximately 6 months. In the ORCHARRD trial the median OS of patients who entered the study with chemorefractory disease was around 10 months, significantly shorter than the median OS of patients enrolled with chemosensitive disease. These data support exploring the use of novel therapies in refractory/early relapsed DLBCL patients (Van Imhoff et al 2017).

Event-free survival is an acceptable primary efficacy endpoint in the setting of aggressive diseases like DLBCL and has shown to be a robust surrogate endpoint for OS in frontline DLBCL trials evaluating immunochemotherapy ([Shi et al 2016](#), [Lee et al 2011](#)). In this trial, EFS is defined as the time from date of randomization to death due to any cause for all patients or lack of response (i.e. PD or SD) at or after the week 12 (± 1 w) assessment.

SD is considered as treatment failure in aggressive B-cell lymphoma and, as was demonstrated by the analysis performed in the CORAL study in patients not responding to first and second salvage therapies (and eventually not receiving HDCT and HSCT), the expected survival is only 3.4 months from the start of the second salvage therapy. The ORCHAARD study also showed that only 33% and 37% of patients in the two treatment groups (R-DHAP and O-DHAP respectively) were able to undergo stem cell transplant ([van Imhoff et al 2017](#)). The current goal of salvage therapy in r/r aggressive B-cell lymphoma patients after front line immunochemotherapy is to achieve a good quality response and perform HDCT and HSCT. As a general rule, if a response is not observed after 2-3 cycles of a first salvage therapy, the recommendation is to change to a new salvage therapy (2nd salvage) with the same objective of achieving a response and eventually perform HSCT. If no response is observed, treatment guidelines recommend use of axicabtagene ciloleucel or another course of 2 cycles of a new salvage therapy (i.e., 3rd salvage), or best supportive care. The possibility of being rescued after 3rd salvage chemotherapy is very low and most patients will die due to quickly progressing disease ([NCCN v3 2018](#), [Van den Neste et al 2017](#)). For this reason, stable disease after 12 weeks (± 1 week) from randomization (which corresponds to approximately 2 rounds of different 2-cycle salvage therapy post randomization) will be considered as event (for both tisagenlecleucel and SOC arms). At or after the week 12 assessment (± 1 week), patients enrolled in the SOC arm will be offered to crossover to tisagenlecleucel after BIRC confirmation of PD or SD. Additionally patients with PR FDG+ disease by local assessment at the Week 12 assessment or after will be able to request a manufacturing slot for potential crossover. Allowing crossover to tisagenlecleucel will confound the assessment of OS, but will ensure the access to a potentially effective therapy in these poor prognosis patients. As the primary EFS endpoint will be evaluated by BIRC, and in order to avoid informative censoring, crossover will only be allowed after PD or SD at or after the week 12 (± 1 week) assessment is confirmed by BIRC.

In addition to the response assessment, three Patient Reported Outcome (PRO) tools, FACT-Lym, SF-36 version 2 and EQ-5D-5L, are proposed for this study as they are considered adequate to support the establishment of clinical benefit for lymphoma patients. FACT-Lym tool will be used to assess disease-specific quality of life. SF-36 v2 will assess general health/quality of life with EQ-5D to assess health utility for the purpose of economic evaluation. Both FACT-Lym and SF-36 v2 have been already used in tisagenlecleucel previous pivotal NHL studies

Safety will be monitored throughout the trial. Per Health Authority guidelines ([FDA 2006](#), [EMA 2009](#)) for gene therapy products or advanced therapy medicinal products that utilize integrating vectors (e.g. lentiviral vectors), all patients treated with tisagenlecleucel must be monitored for specific toxicities for up to a total of 15 years following infusion, irrespective of their response to tisagenlecleucel. All patients who receive tisagenlecleucel will be monitored

in this trial for 5 years, followed by semiannual and annual safety assessments in a separate long-term safety follow-up protocol (CCTL019A2205B) for an additional ten years.

Based on current clinical experience with tisagenlecleucel therapy, acute toxicities are expected in the first 28 days after a single infusion of tisagenlecleucel cells. The main expected acute toxicities include events associated with the elimination of normal CD19 positive B cells, cytokine release syndrome (CRS)/macrophage activation syndrome (MAS) from the onset of antitumor responses mediated by large numbers of activated T cells, tumor lysis syndrome (TLS), neurotoxicity and among others, toxicities associated with the lymphodepleting chemotherapy conditioning regimen used with adoptive T-cell therapy. For more details and guidance on management of these toxicities refer to [Section 6.3](#).

Potential long-term toxicities of tisagenlecleucel therapy may include continued B cell aplasia with increased risk of infections if tisagenlecleucel cells persist. Other potential toxicities may include insertional site oncogenesis, expression of replication competent lentivirus (RCL) detection, and potential effects of maternal tisagenlecleucel cells on pregnancy outcome. RCL, autonomous proliferation of infused tisagenlecleucel T cells, and insertional site oncogenesis during the tisagenlecleucel therapy trials have not been observed to date.

Collection of such long-term effects of tisagenlecleucel therapy will help to further define the risk-benefit profile of tisagenlecleucel in patients with B cell malignancies. These observations will also serve to provide further guidance to patients, health care providers and investigators of such risks and their detection and management.

4.2 Rationale for dose/regimen and duration of treatment

The recommended tisagenlecleucel dose is a single intravenous (i.v.) infusion of $0.6 - 6.0 \times 10^8$ CAR-positive viable T cells, based on available dose-response, dose-safety, and dose-cellular kinetics analyses performed using the data obtained from r/r DLBCL patients (data cut-off date: 8-Mar-2017) in Phase II study (CTL019C2201; JULIET). If bridging chemo therapy prior to tisagenlecleucel infusion is used, duration of treatment should follow local prescribing information. The recommended regimens are outlined in [Section 6.1.1](#) (Control drug). Lymphodepleting chemotherapy should be administered as per [Section 6.1.4](#).

Dose-response and dose-exposure: Across the dose range studied, dose and exposure were independent. Additionally, clinically meaningful responses were observed from 0.6 to 6.0×10^8 CAR-positive viable T cells.

Dose-safety: The probability of any grade neurologic events and time to resolution of cytopenias were not impacted by dose. There was an increase in probability of any grade and grade 3/4 CRS with increasing dose; however, the probability of grade 3/4 CRS was comparable across the dose range of 5.0 to 6.0×10^8 CAR-positive viable T cells. In addition, CRS is generally manageable in the study with the steps outlined in the CRS management algorithm.

Based on the totality of the dose-safety, dose-efficacy, dose-exposure and exposure-response, and considering the positive benefit risk observed across the full range of doses, the following dose specification will be utilized in this study: $0.6 - 6.0 \times 10^8$ CAR-positive viable T cells.

For patients in the control arm, the duration of chemotherapy is determined by response to treatment, tolerability and the treating institution's policies. Investigators should refer to the local prescribing information for each drug.

4.3 Rationale for choice of comparator drugs

The ESMO and NCCN clinical treatment guidelines for patients with relapsed/refractory DLBCL recommend for patients with adequate performance status (defined by age and absence of major organ dysfunctions) a salvage regimen with rituximab and chemotherapy followed in responsive patients by high-dose chemotherapy and autologous HSCT (Tilly et al 2015, NCCN v7 2018). Without autologous HSCT, chemotherapy provides only short-term disease control in r/r DLBCL (Elmstrom et al 2010). For patients with r/r DLBCL failing first line treatment the established SOC treatment strategy is salvage therapy followed by autologous HSCT.

In recent years, 4 regimens have been mainly used as salvage therapy preceding autologous HSCT in patients with r/r DLBCL eligible for autologous HSCT: R-DHAP, R-ICE, R-GDP (Tilly et al 2015), and R-GemOx (Mounier 2013). In the present trial, all patients randomized to SOC therapy will receive one of the above-mentioned 4 regimens as per the treating physician. For patients randomized to the tisagenlecleucel treatment arm, they will have the option of using one of the four treatments as bridging chemotherapy while the patients' tisagenlecleucel product is manufactured. The decision to use bridging chemotherapy is based on investigator decision in the best interest of the patient. The specific dosing regimens of each of the SOC regimens can be found in Section 6.1.1.

Patients who are unable to achieve a response to salvage therapy are not eligible to proceed to HSCT. Treatment options in this population include the following, with or without rituximab: bendamustine, GDP, GemOx, or lenalidomide. Additional treatment options are limited and include, ibrutinib (for non-GCB DLBCL), the anti-CD19 CAR-T therapy axicabtagene ciloleucel, and enrolment in clinical trials of new therapies (Tilly et al 2015, NCCN v7 2018). In the present trial, patients who do not achieve a response to the second line salvage therapy may switch to another salvage regimen at week 6 or to lenalidomide or ibrutinib in an attempt to achieve a response which may allow the patient to proceed to transplant. Patients who are still unable to achieve response at week 12 have the option to crossover to arm A to receive the anti-CD19 CAR-T therapy CTL019.

The use of such regimens and their similarities regarding efficacy in r/r DLBCL are supported by the 3 phase III trials discussed in the background section (i.e., CORAL, NCIC-CTG LY.12 and ORCHARRD)(Refer to Section 1.1.1).

4.4 Rationale for lymphodepletion

Adoptive immunotherapy strategies may be able to capitalize on homeostatic T cell proliferation (Dummer et al 2002), a finding that naive T cells begin to proliferate and differentiate into memory-like T cells when total numbers of naive T cells are reduced below a certain threshold (Goldrath and Bevan 1999, Surh and Sprent 2000). Host lymphodepletion may enhance the effectiveness of adoptively transferred T cells (Dummer et al 2002). Homeostatic T cell proliferation can lead to activation of certain immune cell subsets

(King et al 2004), providing a clue to improved anti-tumor responses. CD8+ T cells can undergo up to seven rounds of cell division after being deprived of contact with antigen presenting cells (Kaeche and Ahmed 2001, van Stipdonk 2001). Lymphodepletion eliminates regulatory T cells and other competing elements of the immune system that act as “cytokine sinks”, enhancing the availability of cytokines such as interleukin IL-7 and IL-15 (Klebanoff et al 2005). Data indicates that the increased antitumor efficacy of adoptive transfer following host conditioning is more than simply “making room” because the quantitative recovery of adoptively transferred T cells in mice reveals that *in vivo* proliferation following adoptive transfer is identical in mice with or without previous irradiation (Palmer et al 2004).

Fludarabine with cyclophosphamide has been the most commonly utilized lymphodepleting regimen with CD19 CAR-T cell therapies. It has been demonstrated that addition of fludarabine to cyclophosphamide increases CAR-T cell expansion and persistence and improves disease free survival (DFS) rates in adult patients with r/r B-ALL (Turtle et al 2015).

In Studies [B2202] and [B2205J] combined data (cut-off dates: 24-Apr-2017 for Study [B2202]; 01-Feb-2016 for Study [B2205J]), 99 of 104 patients received lymphodepleting chemotherapy. Ninety-seven of these 99 patients received fludarabine and cyclophosphamide.

In study [C2201] 92 of 99 patients received lymphodepleting chemotherapy. 73 patients received fludarabine and cyclophosphamide, and 19 received bendamustine.

4.5 Purpose and timing of interim analyses

Not applicable.

4.6 Risks and benefits

Tisagenlecleucel administered to over 400 patients in clinical trials across the dose ranges tested has a well characterized safety profile in pediatric and young adult patients. Overall, it is anticipated that the study benefits of tisagenlecleucel therapy in this study will outweigh the risks.

Appropriate eligibility criteria and specific dose-limiting toxicity definitions (as applicable) are included in this protocol. Recommended guidelines for prophylactic or supportive management of study-drug induced AEs are provided in [Section 6.6.2](#).

The risk to subjects in this trial will be minimized by adherence to the eligibility criteria, close clinical monitoring, and adherence to the recommendations for the management of AEs known to be occur with tisagenlecleucel exposure, periodic review of the safety data by an independent Data Monitoring Committee (DMC), and guidance for the investigators in the [Tisagenlecleucel Investigator’s Brochure].

Safety risks that have been identified with the use of tisagenlecleucel or are considered potentially associated with tisagenlecleucel are briefly outlined below.

4.6.1 Identified safety risks with the use of tisagenlecleucel

Safety risks that have been identified with the use of tisagenlecleucel or are considered potentially associated with tisagenlecleucel are briefly outlined below. For more information, please refer to the [Tisagenlecleucel Investigator's Brochure]

4.6.1.1 Cytokine release syndrome (CRS) / macrophage activation syndrome (MAS)

Cytokine release syndrome (CRS) is an on-target toxicity that is associated with tisagenlecleucel cell expansion, activation and tumor cell killing. It is a result of systemic inflammatory response caused when cytokines are released by activated T cells, including interferon gamma (IFN γ), IL-6 and tumor necrosis factor (TNF). Severe and life-threatening events have been observed in patients treated with tisagenlecleucel. In r/r B-ALL, appeared to be related to tumor burden, early CRS onset and early fever onset. In DLBCL, the probability of developing CRS of grade 3 and 4 in severity CRS was increased with high tisagenlecleucel dose and exposure. In the majority of cases, CRS occurs within the first 2-3 weeks post-infusion and shows a wide range of clinical signs and symptoms (Table 4-1). Macrophage activation syndrome (MAS) is also associated with CRS as manifested by liver function test abnormalities, cytopenias and coagulopathy.

Life-threatening and fatal outcomes associated with CRS and severe concomitant infections have been observed in pediatric and adult patients treated with tisagenlecleucel.

Table 4-1 Clinical signs and symptoms associated with CRS (Lee et al 2014)

Organ system	Symptoms
Constitutional	Fever \pm rigors, malaise, fatigue, anorexia, myalgia, arthralgia, nausea, vomiting, headache
Skin	Rash
Gastrointestinal	Nausea, vomiting, diarrhea
Respiratory	Tachypnea, hypoxemia
Cardiovascular	Tachycardia, widened pulse pressure, hypotension, increased cardiac output (early), potentially diminished cardiac output (late)
Coagulation	Elevated D-dimer, hypofibrinogenemia \pm bleeding
Renal	Azotemia
Hepatic	Transaminitis, hyperbilirubinemia
Neurologic	Headache, mental status changes, confusion, delirium, word finding difficulty or frank aphasia, hallucinations, tremor, dysmetria, altered gait, seizures

A therapeutic strategy for the management of CRS is provided in Section 6.6.2.1 that should be followed.

4.6.1.2 Neurological events

Neurological events have been observed in patients following various types of T cell directed therapy including tisagenlecleucel and other CAR-T cell therapies of other institutions. The pathophysiology for neurotoxicity is not fully understood but thought to be related to generalized T cell mediated inflammation rather than direct toxicity of CAR-T cells on the brain (Tey 2014). Some of the neurological events observed may be related to CRS, but whether this results from systemic cytokines crossing the blood brain barrier and engaging

cytokine receptors in the brain or from direct cytokine production in the CNS is not clear ([Maus et al 2014](#)). There are no clear predictors of neurologic toxicity.

Manifestations of neurological events may include a multifarious set of symptoms and diagnoses including agitation, altered state of consciousness, aphasia, confusion, delirium, disorientation, encephalopathy, headache, mutism, seizures or tremor. Some of the events are severe and may have a life-threatening outcome.

The majority of neurological events were observed within 8 weeks following tisagenlecleucel infusion and were transient; however a delayed onset (i.e. > 8 weeks) may occur.

Notably, the onset of neurological toxicity can be concurrent with CRS, following resolution of CRS or in the absence of CRS. Onset of neurological events may be concurrent with high fever during the development and at the time of maximal grade of CRS. The incidence appeared to be greater with higher CRS severity and prior history of CNS leukemia and history of other prior CNS diseases. Encephalopathy typically occurred after peak CRS symptoms and tended to be self-limiting with some exceptions. A few have occurred after CRS and were not associated with high fevers. Neurologic toxicity does not appear to correlate with CRS severity and was not prevented by tocilizumab.

The causality assessment of neurological events in patients treated with tisagenlecleucel can be confounded as CNS toxicity may be associated with chemotherapy used for lymphodepletion and the presence of comorbid conditions such as CRS, fever and infections.

For the management of neurological events see [Section 6.6.2.2](#).

4.6.1.3 Hypersensitivity including acute infusion reactions

Since tisagenlecleucel is an autologous cellular product, hypersensitivity may occur due to the excipients (such as dimethyl sulfoxide (DMSO) or dextran 40) of the infused solution in which the cells are dispersed. In addition, host immune responses may result from presentation of CAR transgene expressed immunogenic epitopes including murine sequences in the scFv extracellular binding domain (derived from a murine monoclonal antibody) or novel epitopes arising at junctions between components of the CAR fusion polypeptide ([Park et al 2007](#); [Lamers et al 2006](#); [Lamers et al 2007](#); [Lamers et al 2011](#)).

Clinically, hypersensitivity reactions can be classified as 'immediate' or 'delayed' depending on their onset after drug administration ([Corominas et al 2014](#); [Limsuwan and Demoly 2010](#)). **In principle**, immediate reactions including acute infusion reactions occur within less than 1 hour after drug administration and may present in a wide range of symptoms such as fever, chills, nausea, urticaria, angioedema, rhinitis, conjunctivitis, dyspnea, bronchospasm, tachycardia, hypotension, anaphylaxis or anaphylactic shock. Delayed hypersensitivity reactions appear after more than 1 hour and up to several days after drug exposure and could include variable cutaneous symptoms such as late-occurring urticaria, maculopapular eruptions, fixed drug eruptions, vasculitis, toxic epidermal necrolysis, Stevens- Johnson syndrome, or drug reaction with eosinophilia and systemic symptoms (DRESS) ([Averbeck et al 2007](#); [Descotes 2012](#); [Corominas et al 2014](#)).

To date, the majority of events observed after tisagenlecleucel infusion were mild or moderate in severity, manageable and recovered.

Patients will have typically received lymphodepleting chemotherapy that is completed several days prior to tisagenlecleucel infusion. Therefore it should be kept in mind that symptoms and findings at this time may also be the result of the onset of chemotherapy related toxicities.

A therapeutic strategy for the management of hypersensitivity including acute infusion reactions is provided in [Section 6.6.2.3](#).

4.6.1.4 Tumor lysis syndrome (TLS)

Tumor lysis syndrome (TLS) is a potentially life-threatening metabolic disorder that occurs when tumor cells undergo rapid decomposition spontaneously or in response to cytoreductive therapy. It tends to occur particularly with highly effective therapies and in patients with high tumor burden and cancers with a high potential for cell lysis include high-grade lymphomas, acute leukemias, and other rapidly proliferating tumors.

Metabolic abnormalities characteristic of TLS include abnormally high serum uric acid levels (hyperuricemia) resulting from the breakdown of purine-containing nucleic acids and major electrolyte imbalances such as hyperkalemia, hyperphosphatemia, and hypocalcemia. Delayed recognition of the metabolic imbalances caused by the massive release of tumor cell contents may result in clinical complications such as acute kidney injury, seizures, and cardiac arrhythmias ([Mughal et al 2010](#)).

Tumor lysis syndrome was clinically observed in a timely relation to tisagenlecleucel T cell expansion. In the clinical experience with tisagenlecleucel thus far, most cases of TLS had a grade 3 in Common Terminology Criteria for Adverse Events (CTCAE) severity, however, the risk has been moderate to low with appropriate monitoring after lymphodepleting chemotherapy, prophylaxis and treatment as needed.

A therapeutic strategy for the management of TLS is provided in [Section 6.6.2.4](#).

4.6.1.5 Infections

There is an increased risk and severity of infections in patients with longer and more intense immunosuppression. Patients treated with tisagenlecleucel are at risk of infection for several reasons:

- Lymphodepleting chemotherapy prior to treatment with tisagenlecleucel may cause severe neutropenia and B-cell depletion from tisagenlecleucel itself is known to be associated with infections.
- B-cell depletion is known to be associated with hypogammaglobinemia that also contributes to the risk.
- Patient with prolonged and profound immunosuppression may be at enhanced risk for more frequent and severe opportunistic infections
- Underlying bone marrow disease or dysfunction further increases the risk of infections

Serious infections were observed in patients after tisagenlecleucel infusion, some of which were life- threatening or fatal.

A therapeutic strategy for the management of infections is provided in [Section 6.6.2.5](#).

4.6.1.5.1 Viral reactivation

Hepatitis B virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure and death, can occur in patients treated with drugs directed against B cells. Hepatitis cases have been reported in patients who are hepatitis B surface antigen (HBsAg) positive, and also in patients who are HBsAg-negative but hepatitis B core antibody (anti-HBcAb) positive. HBV reactivation has occurred in patients who appear to have resolved hepatitis B infection (i.e., HBsAg-negative, anti-HBc-positive and hepatitis B surface antibody [anti-HBsAb] positive).

HBV reactivation is defined as an abrupt increase in HBV replication manifesting as a rapid increase in serum HBV DNA level or detection of HBsAg in a person who was previously HBsAg-negative and anti-HBc-positive. Reactivation of HBV replication is often followed by hepatitis, i.e., increase in transaminase levels. In severe cases, increase in bilirubin levels, liver failure, and death can occur.

Subjects with active or prior hepatitis B, hepatitis C or human immunodeficiency virus (HIV) confirmed by serology will not be enrolled in the study; for detailed exclusion criteria see [Section 5.2](#) for serology assessment see [Section 16.2](#).

4.6.1.6 Febrile neutropenia

Febrile neutropenia observed with tisagenlecleucel can be caused due to multiple factors, including underlying bone marrow disease, prior chemotherapies, radiation treatments or lymphodepleting chemotherapy, reduced response to growth factors (either exogenous or endogenous) in addition to B-cell aplasia that may favor a production of auto-antibodies binding to the neutrophil surface resulting in neutropenia and also disturb the balance between granulopoiesis and lymphopoiesis in the bone marrow ([Tesfa and Palmblad 2011](#)).

Febrile neutropenia and associated events such as grade 3 or grade 4 decreased neutrophil counts with elevated temperature were reported in clinical studies with tisagenlecleucel. The use of chemotherapy is known to be associated with the risk of neutropenia and if severe, with febrile neutropenia. The risk of neutropenia depends on various factors such as type and dose of chemotherapy used, age, gender, performance status and baseline hematology lab data. As lymphodepleting therapy is used in all patients with a white blood cell (WBC) count >1000 cells/ μ L, febrile neutropenia is seen in patients treated with tisagenlecleucel regimen. Also, as lymphodepleting therapy is given close to the infusion of tisagenlecleucel (within two weeks), therefore, overlapping toxicities can be expected.

A therapeutic strategy for the management of febrile neutropenia is provided in [Section 6.6.2.6](#).

4.6.1.7 Prolonged depletion of normal B cells and agammaglobulinemia

B-cell aplasia is an expected on-target toxicity of a successful CD19-directed CAR T cell therapy and a useful surrogate reflecting the persistence of CAR T cells and effectiveness of treatment. B-cell aplasia has been observed in all responding patients with B-ALL. The AEs observed after tisagenlecleucel infusion were managed well by treatment with immunoglobulins.

Loss of B-cells can result in hypo- to a-gammaglobulinemia, potentially rendering the patients more susceptible to infections, especially with encapsulated organisms; and viral reactivation such as herpes viruses or rarely in progressive multifocal leukoencephalopathy (PML) ([Section 4.6.1.8](#)).

Given that a typical T-lymphocyte may have a lifespan of 40 years, tisagenlecleucel may potentially be detectable in a patient for a very prolonged period and **prolonged** depletion of B-cells may occur, in particular in the subset of patients who continue to demonstrate a tumor response. Long term data are currently not available. A therapeutic strategy for the management of B cell depletion with resulting hypogammaglobulinemia is provided in [Section 6.6.2.7](#).

4.6.1.7.1 Progressive multifocal leukoencephalopathy (PML)

Progressive multifocal leukoencephalopathy is a demyelinating disease of the central nervous system (CNS) associated with reactivation of prior John Cunningham (JC) virus infection. Patients classically present with subacutely with focal neurologic deficits (e.g., weakness, speech difficulties, unsteady gait and hemiparesis), ophthalmic symptoms (e.g., homonymous hemianopia progressing to cortical blindness), personality changes, and cognitive dysfunction. Imaging (CT or MRI) shows lesions in the white matter, most commonly of the occipitoparietal lobe and without mass effect.

A therapeutic strategy for the management of B cell depletion with resulting hypogammaglobulinemia is provided in [Section 6.6.2.7](#).

4.6.1.8 Hematopoietic cytopenias lasting greater than or equal to 28 days

Hematopoietic cytopenias are an on-target effect after tisagenlecleucel infusion and activity of tisagenlecleucel on normal B-cells.

Patients treated with tisagenlecleucel may exhibit hematopoietic cytopenias for several weeks an on-target effect after tisagenlecleucel exposure and as sequelae of bridging and lymphodepleting chemotherapy. Prolonged neutropenia has been associated with increased risk of infection. Myeloid growth factors, particularly granulocyte-macrophage colony stimulating factor (GM-CSF), are not recommended during the first 3 weeks after tisagenlecleucel or until CRS has resolved.

A therapeutic strategy for the management of hematopoietic cytopenias is provided in [Section 6.6.2.8](#).

4.6.2 Potential safety risks

Thus far, an association with the potential safety risks briefly described below and tisagenlecleucel have not been confirmed. However, these topics are being closely monitored due to their clinical relevance.

4.6.2.1 Cerebral edema

Fatal cases of cerebral edema, soon after infusion with rapid evolution, have been reported with CAR-T cell therapies other than tisagenlecleucel; in five patients in the Rocket study evaluating JCAR015 for the treatment of ALL and in one patient in the Zuma-1 study

evaluating KTE-19 for the treatment of CLL. The patient in the Zuma-1 study is described as becoming febrile on Day 1 and progressing from grade 3 to grade 4 CRS, refractory to tocilizumab and dexamethasone, by Day 4. Cerebral edema developed on Day 9, was refractory to siltuximab and mannitol, and led to death on Day 11 ([Turtle et al 2017](#)).

To date there have been no such cases reported for tisagenlecleucel.

4.6.2.2 Replication competent lentivirus (RCL) production

Replication-competent lentivirus (RCL) may be generated during tisagenlecleucel manufacturing using a lentiviral vector to encode anti-CD19 CAR or subsequently after introduction of vector transduced viable T cells into the patient.

However, an RCL resulting from manufacturing is highly unlikely since elements are incorporated in the design of the vector system that minimize vector recombination and generation of RCL. Furthermore, the vector used to transduce the product undergoes sensitive assays for detection of RCL. Thus patients will only receive cell products that meet RCL release criteria considered sufficient to confirm the absence of RCL in tisagenlecleucel and the negligible probability of *de novo* generation of any RCL.

No AEs related to generation of RCL were noted post-infusion in the tisagenlecleucel development program. However, generation of an RCL following tisagenlecleucel infusion remains a theoretical possibility. The development of RCL could pose a risk to both the patients and their close contact(s), and therefore, monitoring for RCL will be conducted during the course of the trial (see [\[Investigational Product Handling Manual\]](#) for a description of the assays). Since the probability and characteristics of an RCL are unknown, no regulatory guideline for the management of RCL positive subjects exist to date.

As per guidance for gene therapy medicinal products, patients exposed to tisagenlecleucel will be monitored for 15 years following last treatment for vectors persistence and RCL within the long-term follow-up study.

The management of this potential risk is addressed in [Section 6.6.2.9](#).

4.6.2.3 New or secondary malignancies (including vector insertion site oligo/monoclonality)

Insertion of lentiviral vector sequences throughout the genome has the potential to dysregulate local host cell gene expression with a theoretical risk of insertional oncogenesis resulting from disruption of normal function of genes that control cell growth and potential risk of development of secondary malignancies.

Vector-mediated insertional mutagenesis and subsequent malignant cell transformation after gene correction based on autologous HSC gene therapy has been observed in X-linked severe combined immunodeficiency (SCID-X1), chronic granulomatous disease (CGD), and Wiskott-Aldrich syndrome (WAS), where first-generation gamma-retroviral vectors harboring long terminal repeats (LTRs) with strong enhancer/promoter sequences were used ([Hacein-Bey-Abina et al 2003](#), [Howe et al 2008](#), [Boztug et al 2010](#), [Stein et al 2010](#), [Persons and Baum 2011](#)).

In contrast, tisagenlecleucel uses third generation self-inactivating lentiviral vector. Insertional mutagenesis was addressed in two lentivirus insertion site analysis (LISA) studies where 12 batches of manufactured patient product ready for infusion and two batches of product manufactured from healthy donor cells were analyzed. The results indicate that there was no preferential integration near genes of concern, no preferential sites of integration (hot spots), and no preferential outgrowth of cells harboring integration sites of concern.

Tisagenlecleucel is based on autologous, fully differentiated T cells and therefore the carcinogenicity risk is considered to be low in comparison to genetic modification or repair such as HSC. In a recent review of CAR-T cell therapies, (Bonifant et al 2016) as well as (Mohanlal et al 2016) discussed that to date no cases of malignant transformation have been reported for genetic modification of T cells and that there currently is no evidence for vector-induced immortalization, clonal expansion, or enrichment for integration sites near genes implicated in growth control or transformation. This is supported by the results of the lentivirus insertion site analysis (LISA) studies performed during the development of tisagenlecleucel.

Theoretically, CAR-positive viable T cells could proliferate without control of normal homeostatic mechanisms. In pre-clinical studies (Milone et al 2009) and clinical experience to date (Porter et al 2011, Grupp et al 2013, Maude et al 2014), CAR-positive viable T cells have only proliferated in response to physiologic signals or upon exposure to CD19 antigen. In the context of tisagenlecleucel therapy, it is expected that the T cells will proliferate in response to signals from the CD19 expressing malignant tumor and normal B cells. This could be either harmful depending on the extent of proliferation or beneficial, since clonal dominance of adoptively transferred T cells has been associated with tumor reduction in adoptive transfer trials (Dudley et al 2002, Dudley et al 2005).

The management of this potential risk is addressed in [Section 6.6.2.10](#).

4.6.2.4 Exacerbation of an existing or new incidence of autoimmune disease

The risk of autoimmune reaction with tisagenlecleucel is low since CD19 is not present on most normal tissue other than normal B-cells. New incidence or exacerbation of an autoimmune disorder has not been observed with tisagenlecleucel thus far. However, instances of new or exacerbation were reported in the literature, both for diseases without an obvious underlying autoimmune cause such as stroke (Kamel and Iadecola 2012) and for ones with a clear autoimmune basis such as multiple sclerosis and optic neuritis (Feldman et al 2015). Both cellular and cytokine driven exacerbations have been observed in patients receiving chemotherapy; CNS autoimmune disorders (such as optic neuritis) have been reported to be exacerbated by both mechanisms (Skaper et al 2014, Cramer et al 2015). In addition, the use of tocilizumab, a monoclonal antibody against the IL-6 receptor, can exacerbate demyelinating disease, and therefore its use is to be used with precaution in cases of demyelinating disease (Actemra® USPI). Prior chemotherapy and radiation also contribute to the risk.

No AEs associated with this potential were observed in tisagenlecleucel clinical trials.

4.6.2.5 New incidence of a hematologic disorder

There is potential risk of a hematologic disorder such as myelodysplastic syndrome, aplastic anemia or bone marrow failure, given that tisagenlecleucel is a genetically modified cell product that may have the potential to affect hematopoietic cell function, as could prior chemotherapy and radiation given for the underlying malignancy.

4.6.2.6 New incidence or exacerbation of an existing neurological event

Neurological events are an identified risk for tisagenlecleucel (see [Section 4.6.1.2](#)). Underlying neurological disorders may become exacerbated by chemotherapy, lymphodepletion or subsequent immunosuppression of tisagenlecleucel treatment. There is currently no evidence that tisagenlecleucel is associated with exacerbation of an existing neurological event.

4.6.2.7 Graft versus host disease (GVHD)

The chance of graft versus host disease (GVHD) occurring in patients is low, but it is a potential risk with tisagenlecleucel therapy in patients with mixed chimerism of host and donor hematopoietic cells due to prior allogeneic HSCT. A study of activated donor lymphocyte infusions (ex vivo activated cells collected from the donor and grown in the same fashion as tisagenlecleucel but without the CAR introduction) did not show high rates of GVHD (2/18 patients with grade 3 GVHD and none with grade 4) ([Porter et al 2006](#)). Of 18 ALL patients treated with autologous tisagenlecleucel therapy who had relapsed after prior allogeneic HSCT with residual mixed chimerism, none have developed GVHD after autologous tisagenlecleucel infusion ([Maude et al 2014](#)). Long term data are currently limited.

For the management of GVHD see [Section 6.6.2.11](#).

4.6.3 Other risks

4.6.3.1 Pregnancy, lactation, and effects on fertility

No preclinical reproductive studies have been conducted with tisagenlecleucel to assess whether it can cause fetal harm when administered to a pregnant woman. There is a potential risk that immunologically active maternal tisagenlecleucel positive T cells may cross the placenta. The survival of normal maternal cells in the fetus is usually limited owing to effective rejection by an immunocompetent target. However maternal cells can persist in immunocompetent offspring into adult life (maternal microchimerism (MMc)). MMc has been observed in healthy fetus and adults, and was observed in up to 42% of cord blood samples from healthy newborns ([Muller et al 2001](#)). The persistence of maternal cells in offspring's tissues and circulation has been associated with autoimmune disorders. The histocompatibility antigens (HLA) disparity between mother and fetus has been hypothesized as responsible for the pathogenesis of some auto-immune diseases.

Maternal CD19 CAR T cells may be expected to cross the placental barrier and potentially exhibit MMc similar to that of normal T cells. The impact on the offspring's B cells is unknown. Therefore, tisagenlecleucel is not recommended for women who are pregnant, and pregnancy after tisagenlecleucel administration should be discussed with the treating

physician. No data are currently available to determine the duration of contraception after receiving tisagenlecleucel. It is also not known whether tisagenlecleucel can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity.

The testicular environment is usually immunosuppressive to T cells, leading to control and low numbers of T lymphocytes including CD19 CART cells ([Hedger and Meinhardt 2000](#)). If transferred to female reproductive tract along with sperm, T cells are likely to be recognized as non-self by the female immune system and therefore be destroyed. A fundamental risk may arise from the presence of RCL the female organism may be exposed to after sexual intercourse. However, the principal design of the vector and the analytic measures taken during manufacturing of tisagenlecleucel will exclude the presence of RCL with highest probability, and the female risk for exposure to tisagenlecleucel and/or RCL is considered extremely low.

As it is also not known whether tisagenlecleucel can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity, tisagenlecleucel should not be administered to pregnant women and care should be taken to avoid conceptions.

Therefore, women of child bearing potential (WOCBP), defined as all women physiologically capable of becoming pregnant, and sexually active males are excluded from clinical trials with tisagenlecleucel unless they use adequate contraception. No data are currently available to determine the duration of contraception after receiving tisagenlecleucel.

WOCBP and sexually active males must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study, and agree that in order to participate in the study they must adhere to the contraception requirements outlined in the exclusion criteria. If there is any question that the subject will not reliably comply, they should not be entered or continue in the study.

There is no information regarding the presence of tisagenlecleucel in human milk, the effect on the breast-fed child or the effects of tisagenlecleucel on milk production. Nursing women are excluded from participation in this study.

4.6.3.2 Risks associated and with SOC immunochemotherapy

The toxicities of SOC treatment are widely described in [Gisselbrecht et al \(2010\)](#), [Crump et al \(2014\)](#), [Tilly et al \(2015\)](#), [Van den Neste et al \(2016\)](#), [Van Imhoff et al \(2017\)](#), [Van den Neste et al \(2017\)](#). Preventive measures, monitoring and management of toxicities should be managed as per local standard of care.

5 Population

The target population consists of adult subjects with aggressive NHL who are refractory or relapsed within 365 days of their last dose of first line immunochemotherapy and eligible for stem cell transplant (SCT). Approximately 318 subjects will be randomized for treatment. It is anticipated that the life expectancy of randomized patients is at least 12 weeks.

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 Inclusion criteria

Subjects eligible for inclusion in this study must meet **all** of the following criteria:

1. Signed informed consent must be obtained prior to participation in the study.
2. Patients must be ≥ 18 years of age at the time of informed consent form (ICF) signature.
3. Histologically confirmed (by local histopathological assessment), aggressive B-cell NHL at relapse/progression after front line therapy. Aggressive B-cell NHL is heretofore defined by the following list of subtypes ([Swerdlow et al 2016](#)):
 - DLBCL, NOS
 - FL grade 3B,
 - Primary mediastinal B cell lymphoma (PMBCL),
 - T cell rich/histiocyte rich large B cell lymphoma (T/HRBCL),
 - DLBCL associated with chronic inflammation,
 - Intravascular large B-cell lymphoma,
 - ALK+ large B-cell lymphoma,
 - B-cell lymphoma, unclassifiable, (with features intermediate between DLBCL and classical HL),
 - High grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements,
 - High grade B-cell lymphoma, NOS
 - HHV8+ DLBCL, NOS
 - DLBCL transforming from follicular lymphoma
 - DLBCL transforming from marginal zone lymphoma
 - DLBCL, leg type
4. Relapse or progression within 365 days from last dose of rituximab and anthracycline containing first line immunochemotherapy or refractory (have not achieved a CR or PR).
5. Patient is considered eligible for ASCT as per local investigator assessment. **Note:** Intention to transplant and type of HDCT regimen will be documented in the IRT system and in the eCRF.
6. Measurable disease:
 - Nodal lesions >15 mm in the long axis, regardless of the length of the short axis, and/or
 - Extranodal lesions (outside lymph node or nodal mass, but including liver and spleen) >10 mm in long AND short axis
7. ECOG performance status 0 or 1
8. Adequate organ function:
 - a. Renal function defined as:
 - Serum creatinine of $\leq 1.5 \times \text{ULN}$, OR $\text{eGFR} \geq 60 \text{ mL/min/1.73 m}^2$
 - b. Hepatic function defined as:
 - ALT and AST $\leq 5 \times \text{ULN}$

- Bilirubin ≤ 2.0 mg/dl with the exception of patients with Gilbert syndrome who may be included if their total bilirubin is $\leq 3.0 \times \text{ULN}$ and direct bilirubin $\leq 1.5 \times \text{ULN}$
- c. Hematologic Function (regardless of transfusion) defined as:
 - Absolute neutrophil count (ANC) $> 1000/\text{mm}^3$
 - Absolute lymphocyte count (ALC) $> 300/\text{mm}^3$ and absolute number of CD3+ T cells $> 150/\text{mm}^3$
 - Platelets $\geq 50,000/\text{mm}^3$
 - Hemoglobin > 8.0 g/dl
- d. Adequate pulmonary function defined as:
 - No or mild dyspnea (\leq Grade 1)
 - Oxygen saturation measured by pulse oximetry $> 91\%$ on room air
 - Forced expiratory volume in 1 s (FEV1) $\geq 50\%$ or carbon monoxide diffusion test (DLCO) $\geq 50\%$ of predicted level
- 9. Must have a leukapheresis material of non-mobilized cells available for manufacturing.
Note: Please refer to [Section 6.2.2](#), [Section 8.1](#) (Leukapheresis) for prohibited concomitant medications and washout times to ensure adequate collection as well as the [\[Investigational Leukapheresis, Cryopreservation, and Scheduling Manual\]](#) for specific collection procedures.

5.2 Exclusion criteria

1. Patients with Epstein Barr Virus positive (EBV+) DLBCL, NOS, Richter's transformation, and Burkitt lymphoma, and primary DLBCL of CNS
2. Prior treatment with anti-CD19 therapy, adoptive T-cell therapy, or any prior gene therapy product
3. Treatment with any lymphoma-directed second line anticancer therapy prior to randomization. Only steroids are permitted for disease control.
4. Patients with active CNS involvement are excluded, except if the CNS involvement has been effectively treated (i.e. patient is asymptomatic) and local treatment was > 4 weeks before randomization
5. Prior allogeneic HSCT
6. Investigational medicinal product (IMP) within the last 30 days prior to screening **Note:** IMPs should not be used at any time while on study until the first progression following tisagenlecleucel infusion
7. Presence of active or prior hepatitis B or C as indicated by serology (for detailed criteria see [Section 16.1](#) Appendix 1). Serology must be repeated, if the interval between testing prior to lymphodepletion and tisagenlecleucel infusion exceeds 8 weeks.
8. HIV positive patients. Serology must be repeated, if the interval between testing prior to lymphodepletion and tisagenlecleucel infusion exceeds 8 weeks.
9. Uncontrolled acute life threatening bacterial, viral or fungal infection (e.g. blood culture positive ≤ 72 hours prior to randomization)
10. Any of the following cardiovascular conditions:

- a. Unstable angina, myocardial infarction, coronary artery bypass graft (CABG), or stroke within 6 months prior to screening,
 - b. LVEF <45% as determined by ECHO or MRA or MUGA at screening or within the past 12 months.
 - c. NYHA functional class III or IV ([Chavey et al 2001](#)), at screening or within the past 12 months.
 - d. Clinically significant cardiac arrhythmias (e.g., ventricular tachycardia), complete left bundle branch block, high-grade AV block (e.g., bifascicular block, Mobitz type II) and third degree AV block, unless adequately controlled by pacemaker implantation.
 - e. Resting QTcF ≥ 450 msec (male) or ≥ 460 msec (female) at screening or inability to determine the QTcF interval
 - f. Risk factors for Torsades de Point (TdP), including uncorrected hypokalemia or hypomagnesemia, history of cardiac failure, or history of clinically significant/symptomatic bradycardia, or any of the following:
 - i. Long QT syndrome, family history of idiopathic sudden death or congenital long QT syndrome
 - ii. Concomitant medication(s) with a “Known Risk of Torsades de Point” per www.qtdrugs.org that cannot be discontinued or replaced by safe alternative medication
11. Previous or concurrent malignancy with the following exceptions:
- a. Adequately treated basal cell or squamous cell carcinoma (adequate wound healing is required prior to study entry)
 - b. *In situ* carcinoma of the cervix or breast, treated curatively and without evidence of recurrence for at least 3 years prior to the study
 - c. A primary malignancy which has been completely resected and in complete remission for ≥ 5 years
12. Intolerance to the excipients of the tisagenlecleucel cell product
13. Patients with active neurological autoimmune or inflammatory disorders (e.g., Guillain-Barré Syndrome (GBS), Amyotrophic Lateral Sclerosis (ALS))
14. Pregnant or nursing (lactating) women
- Note:** Women of child-bearing potential must have a negative serum or urine pregnancy test performed within 24 hours before leukapheresis, lymphodepletion and prior to tisagenlecleucel infusion and SOC therapy.
15. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, **unless** they are using highly effective methods of contraception while taking study treatment and for at least 12 months after the tisagenlecleucel infusion and until CAR T-cells are no longer present by qPCR on two consecutive tests. Highly effective contraception methods include:
- Total abstinence (when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
 - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy, or tubal ligation at least six weeks before taking

study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment

- Male sterilization (at least 6 months prior to screening). For female subjects on the study, the vasectomized male partner should be the sole partner for that subject
- Use of oral, (estrogen and progesterone), injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS), or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception.

In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking study treatment.

Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

Note: If local regulations deviate from the contraception methods listed above to prevent pregnancy, local regulations apply and will be described in the ICF.

16. Sexually active males who do not use a condom during intercourse while taking study treatment and for at least 12 months after the tisagenlecleucel infusion and until CAR T-cells are no longer present by qPCR on two consecutive tests. A condom is required for **all** sexually active male participants to prevent them from fathering a child AND to prevent delivery of study treatment via seminal fluid to their partner. In addition, male participants must not donate sperm for the time period specified above.
17. Subjects enrolled in this study are not permitted to participate in additional parallel investigational drug or device studies.

No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible subjects.

6 Treatment

6.1 Study treatment

6.1.1 Investigational and control drugs

Investigational Drug

For patients randomized to Arm A (tisagenlecleucel) who require optional bridging therapy, the investigator must choose one of the four regimens described under the control arm. Tisagenlecleucel is an autologous cellular immunotherapy product that is comprised of CD3+ T cells that have undergone *ex vivo* T cell activation, gene modification, expansion and formulation in infusible cryomedia.

For details please refer to the [\[Investigational Product Handling Manual and Investigational Product Transport Manual\]](#) and the current version of the [\[Tisagenlecleucel Investigator's Brochure\]](#).

Control Drug (Standard of Care)

For patients randomized to Arm B (SOC therapy), investigators are to choose one of the following regimens.

Rituximab (375 mg/m² starting on the first day prior to chemotherapy on each cycle),

- R-ICE: etoposide (100 mg/m² per day) on days 1 through 3, ifosfamide (5,000 mg/m²) infused continuously for 24 hours on day 2 with mesna, carboplatin (area under the curve (AUC) = 5; maximum dose, 800 mg) on day 2 ([Kewalramani et al 2004](#)). Cycles repeated every 21 days.
- R-DHAP: cisplatin (100 mg/m²) on day 1 via continuous 24-hour infusion, followed on day 2 by cytarabine (2 g/m²) in a 3-hour infusion repeated after 12 hours, dexamethasone (40 mg/d) for 4 consecutive days ([Velasquez et al 1998](#)). Cycles repeated every 21 days.
- R-GDP: gemcitabine 1000 mg/m² on days 1 and 8, cisplatin 75 mg/m² on day 1, dexamethasone (40 mg/d) for 4 consecutive on days 1 through 4 ([Baetz et al 2003](#)). Cycles repeated every 21 days.
- R-GemOx - gemcitabine and oxaliplatin at the doses of 1000 mg/m² and 100 mg/m², respectively, on day 2. ([Mounier et al 2013](#)). Cycles repeated every 15 days.

For patients randomized to Arm B (SOC therapy), a change in therapy is allowed after the Week 6 evaluation if the patient is a non-responder or has a suboptimal response and change in treatment is in the best interest of the patient. Investigators should choose one of the four regimens above or treatment with ibrutinib or lenalidomide.

For patients proceeding to autologous HSCT, mobilization of stem cells will be performed during cycle 2 and/or cycle 3 of salvage therapy according to local policy using granulocyte-colony stimulating factor (G-CSF). In the case of a mobilization failure, additional attempts at mobilization or operative bone marrow harvest can be performed according to local policy. Leukapheresis and cryopreservation will be performed according to local procedures.

Subjects with CR or PR after the 6 weeks (SOC 1) of salvage therapy and adequate stem cell collection should receive high dose chemotherapy approximately 4-6 weeks after the last cycle of salvage therapy. Subjects with PR after cycle 2 may proceed to HDCT according to the judgment of the investigator. In countries where the drugs are available, and can be used for this indication, the BEAM regimen is to be used. BEAM is recommended to be dosed as follows (days shown are relevant to HSCT):

- Carmustine 300 mg/m² i.v., Day -6,
- Etoposide 200 mg/m² i.v., Day -5, -4, -3, -2
- Cytarabine 200 mg/m² every 12 hours (q12hr, 2 doses) i.v., Day -5, -4, -3, -2,
- Melphalan 140 mg/m² i.v., Day -1

If BEAM is not used, the HDT regimen will be in accordance with local policy. Before any subjects are randomized, the HDT regimen must be documented in the institutional treatment policy. The procedure for ASCT will be in accordance with local policy. Prophylaxis of CNS

disease using intrathecal dosing of cytotoxic regimens is permitted and will be according to local policy.

For patients in PR with FDG+ disease at or after the Week 12 local assessment, the site may request a manufacturing slot for potential crossover to tisagenlecleucel.

6.1.2 bPre-infusion evaluation

If any of the following criteria is met tisagenlecleucel infusion must be delayed until resolution. If the period of delay is more than 4 weeks from completing lymphodepletion and there is no significant cytopenia (see [Section 6.1.4.2](#)) lymphodepletion should be repeated, and these criteria will need to be re-checked prior to tisagenlecleucel infusion.

1. Rapidly progressing primary disease
2. Clinical evidence of CNS involvement by primary disease
3. Laboratory abnormalities that, in the opinion of the investigator, may impact subject safety or the subjects' ability to receive tisagenlecleucel.
4. Following clinical abnormalities:
 - Pulmonary: Requirement for supplemental oxygen to keep saturation greater than 90% or presence of progressive radiographic abnormalities on chest x-ray
 - Cardiac arrhythmia not controlled with medical management
 - Hypotension requiring vasopressor support
 - Active infection, as evidenced by positive blood cultures for bacteria, fungi, or polymerase chain reaction (PCR) positivity for viral DNA in blood within 72 hours of tisagenlecleucel cell infusion, or clinical or radiographic evidence
5. A significant change in clinical status that would, in the opinion of the investigator, increase the risk of adverse events associated with tisagenlecleucel
6. Concomitant medications as described in [Section 6.2.1](#).
7. Positive influenza test within 10 days prior to tisagenlecleucel infusion (please refer to [Table 8-2](#)).

Note: If the subject is positive for influenza, oseltamivir phosphate or zanamivir should administered for 10 days as preventative treatment (see Tamiflu® or Relenza® package insert for dosing). The subject must complete their 10 day preventative treatment course **prior** to receiving tisagenlecleucel. The test does not need to be repeated prior to tisagenlecleucel infusion however if flu-like or respiratory signs and symptoms are present, tisagenlecleucel infusion should be delayed until the subject is asymptomatic. For subjects residing in the United States, Canada, Europe and Japan, influenza testing is required during the months of October through May (inclusive). For subjects residing in the southern hemisphere such as Australia, influenza testing is required during the months of April through November (inclusive). For subjects with significant international travel, both calendar intervals above may need to be considered.

6.1.3 Additional safety procedures prior to tisagenlecleucel infusion

Tumor lysis syndrome (TLS)

The risk of tumor lysis syndrome (TLS) is dependent on disease burden. Subjects will be closely monitored both before and after lymphodepleting chemotherapy and the tisagenlecleucel infusion, including blood tests for potassium and uric acid. Subjects with elevated uric acid or high tumor burden will receive prophylactic allopurinol, or a non-allopurinol alternative (e.g. febuxostat).

Infections

Infection prophylaxis with regard to lymphodepletion and other additional treatments should follow local guideline. Infection prophylaxis is not recommended in the setting of tisagenlecleucel infusion.

Cytokine Release Syndrome

Prior to tisagenlecleucel infusion two doses of tocilizumab per subject (for the first 3 weeks after tisagenlecleucel infusion) must be confirmed as available by the local pharmacy and must be available for infusion within 2 hours of physician order for the management of CRS related adverse events (see [Section 6.3.1](#) for details).

Premedication

Side effects from T cell infusions can include fever, chills and/or nausea. All subjects should be pre-medicated with acetaminophen (paracetamol) and diphenhydramine or another H1 antihistamine approximately 30 to 60 minutes prior to infusion. These medications can be repeated every 6 hours as needed. Non-steroidal anti-inflammatory medication may be prescribed if the subject continues to have fever not relieved with acetaminophen (paracetamol). Steroids should NOT be used for premedication. It is recommended that subjects NOT receive systemic corticosteroids other than physiologic replacement, except for serious emergency, since this may have an adverse effect on tisagenlecleucel cell expansion and function. For more information on managing toxicities related to tisagenlecleucel treatment, please refer to [Section 6.3](#).

Supportive care

Local guidelines will be followed for the supportive care of immunosuppressed and chemotherapy treated subjects. All blood products administered should be irradiated. For details about prohibited concomitant medications and non-drug therapies please refer to [Section 6.2.2](#).

6.1.4 Additional study treatments

6.1.4.1 Optional bridging therapy

For patients randomized to Arm A (tisagenlecleucel), there will be an estimated delay of treatment while tisagenlecleucel is manufactured and before it is available on-site. During this time, the treating physician will have the option to treat the patient according to local guidance, product label, and the medical condition of the patient. If bridging therapy is prescribed, the investigator should use one of the four prescribed regimens in [Section 6.1.1](#).

During this optional bridging therapy period, all safety evaluations should follow local standard of care guidelines and be captured in source documentation or database where denoted by [Table 8-2](#).

If optional bridging therapy is interrupted or delayed, the reason must be documented in source files and captured in the appropriate eCRF.

The start of bridging chemotherapy visit start should be registered in IRT.

6.1.4.2 Lymphodepleting chemotherapy

Prior to tisagenlecleucel infusion, each patient should undergo lymphodepletion, unless the patient has a significant cytopenia (e.g. WBC <1,000 cells/ μ L, absolute lymphocyte count <200/ μ L) or any condition that, in the investigator's opinion, precludes lymphodepletion.

If lymphodepleting chemotherapy is NOT required, a visit should still occur during this time window, and required assessments according to [Table 8-2](#) should be completed.

The lymphodepleting chemotherapy visit start should be registered in IRT.

Lymphodepletion should start one week before tisagenlecleucel infusion, which means that tisagenlecleucel will be infused 2 to 6 days after lymphodepletion depending on the lymphodepleting regimen. Lymphodepletion may be repeated in case tisagenlecleucel has been delayed by more than 4 weeks (see [Section 6.1.4.1](#)). The preferred regimen is as follows:

- Fludarabine (25 mg/m² intravenously [i.v.] daily for 3 doses)
- Cyclophosphamide (250 mg/m² i.v. daily for 3 doses starting with the first dose of fludarabine)

Note: Side effects of fludarabine can include severe nervous system events of seizure, agitation, blindness, coma and death. Instances of life-threatening and sometimes fatal autoimmune phenomena such as hemolytic anemia, autoimmune thrombocytopenia/thrombocytopenic purpura (ITP), Evans syndrome, and acquired hemophilia have been reported to occur after one or more cycles of treatment with fludarabine phosphate injection. It may also severely decrease bone marrow function ([Fludarabine full prescribing information](#)).

Cyclophosphamide toxicities include cardiac dysfunction. Acute cardiac toxicity has been reported with doses as low as 2.4 g/m² to as high as 26 g/m², usually as a portion of an intensive antineoplastic multi-drug regimen or in conjunction with transplantation procedures. In a few instances with high doses of Cyclophosphamide, severe, and sometimes fatal, congestive heart failure has occurred after the first Cyclophosphamide dose. Severe marrow suppression is seen and occasional anaphylactic reactions have been reported. Hemorrhagic cystitis, pulmonary toxicity (pneumonitis, pulmonary fibrosis and pulmonary veno-occlusive disease leading to respiratory failure) and veno-occlusive liver disease may occur ([Cyclophosphamide full prescribing information](#)).

If there was previous grade IV hemorrhagic cystitis with cyclophosphamide, or the patient demonstrated resistance to a previous cyclophosphamide-containing regimen, then the following regimen should be used:

- Bendamustine 90 mg/m² i.v. daily for 2 days

Note: Side effects of bendamustine include severely decreased bone marrow function, nausea, vomiting and diarrhea; jaundice may occur, including without other signs of hepatic dysfunction. Fatal and serious cases of liver injury have been reported ([Bendamustine full prescribing information](#)).

No other regimen is allowed for lymphodepletion.

Female patients of childbearing potential must have a negative serum pregnancy test within 24 hours prior to the start of lymphodepleting therapy. If the patient does not require lymphodepleting therapy, she should still have a negative pregnancy test at the required visit that takes place within 5 days from tisagenlecleucel infusion.

6.1.5 Treatment arms

Subjects will be assigned at the randomization visit to one of the following 2 treatment arms/groups in a ratio of 1:1.

- **Arm A:** A single dose of 0.6 to 6.0×10^8 of autologous tisagenlecleucel transduced T-cells administered via intravenous infusion. The patient may also have 3 days of lymphodepleting chemo prior to tisagenlecleucel infusion as described in [Section 6.1.4.1](#). Optional platinum based bridging immunochemotherapy can be given during the time period while tisagenlecleucel is being manufactured (after randomization and prior to lymphodepleting chemotherapy) as per investigator assessment as described in [Section 6.1.4.2](#).
- **Arm B:** SOC immunochemotherapy including, in suitable patients, autologous stem cell transplant, as per local guidelines. Ibrutinib and lenalidomide are also allowed for non-responding patients or patients with suboptimal response at week 6.

6.1.6 Treatment duration

For patients randomized to Arm A, a single dose of tisagenlecleucel will be administered. Prior to tisagenlecleucel infusion, patients may receive optional bridging chemotherapy while tisagenlecleucel is manufactured, and then may receive lymphodepleting chemotherapy as outlined in [Section 6.1.4.1](#).

Patients randomized to Arm B will continue to receive immunochemotherapy as per local guidelines or until patients undergo autologous HSCT.

Patients will continue treatment in Arm B until they experience any of the following:

- Disease progression or continuous SD at or after the week 12 (± 1 week) assessment (confirmed by the BIRC).

Note: All patients who have disease progression or continuous SD at or after the week 12 (± 1 week) assessment determined by the local investigator will require an expedited tumor response review (within 5 business days) by the BIRC. SOC chemotherapy will continue until progressive disease or continuous SD at or after the week 12 (± 1 w) assessment has been confirmed by the BIRC if clinically acceptable. In cases of discordance (i.e., BIRC does not confirm the site's assessment) for as long as it is clinically acceptable the patient should not be discontinued from study treatment.

- Start of a new experimental (i.e., patient is enrolled in a clinical trial) anti-cancer therapy after the week 12 (± 1 week) assessment
- Pregnancy
- Treatment is discontinued at the discretion of the investigator or patient
- Lost to follow-up
- Death
- Study terminated by Sponsor

Patients, that have discontinued early for reasons other than BIRC confirmed PD or continuous SD at or after the week 12 (± 1 week) assessment, loss to follow-up, death, or study termination, will continue efficacy assessments as per protocol until BIRC confirmation of EFS event.

6.1.7 Dosing regimen

Tisagenlecleucel

For patient randomized to the tisagenlecleucel, the recommended dose will consist of a single intravenous (i.v.) infusion of $0.6 - 6.0 \times 10^8$ CAR-positive viable T cells.

In rare cases tisagenlecleucel may present with out-of-specification results of the release testing. Where the administration of the product is necessary to avoid an immediate significant hazard to the patient and taking into account the alternative options for the patient and the consequences of not receiving tisagenlecleucel, the supply of the product may be justified upon request from the treating physician. Tisagenlecleucel will then be provided based on the evaluation of the risks and the confirmation of the treating physician to accept the product.

Tisagenlecleucel infusion will begin 2 to 6 days after completion of lymphodepleting chemotherapy.

The day of (but prior to) the tisagenlecleucel infusion, patients will undergo assessments described in [Table 8-2](#). Final tisagenlecleucel infusion pre-requisites (including an ECG and a rapid influenza test) will be checked prior to infusion as per [Section 6.1.2](#).

Tisagenlecleucel transduced T cells will be given as a single dose within 0.6 to 6.0×10^8 tisagenlecleucel transduced cells. Vital signs will be monitored before, during, and following tisagenlecleucel infusion (per [Table 8-5](#)). An additional blood sample will be collected post-infusion for tisagenlecleucel cellular kinetics assessment as per [Table 8-10](#) and [Table 8-11](#).

The tisagenlecleucel infusion visit should be registered in IRT. If the patient is not infused with tisagenlecleucel, the reason for not infusing should be recorded in IRT.

Standard of Care

For the SOC immunochemotherapy administration, please follow the approved label, required country, and institution guidelines for one of the four prescribed regimens in [Section 6.1.1](#).

Modifications to the dose or regimen based on individual patient tolerability and institution's policy are allowed. If SOC therapy is interrupted or delayed, the reason must be documented in source files and captured in the appropriate eCRF.

The start of SOC visit should be registered in IRT.

6.2 Other treatment(s)

6.2.1 Concomitant therapy

Clinically significant prescription and nonprescription medication, excluding vitamins, and herbal and nutritional supplements, and procedure-related (inpatient or outpatient) medications taken by the subject during the 30 days prior to screening will be recorded, as required by the modified reporting criteria in [Section 16.3](#) Appendix 3.

At every visit following the screening visit up to the end of the study, concomitant medications will be recorded in the medical record and on the appropriate CRF.

A safety follow-up visit should occur 8 weeks after last treatment administration or prior to starting new anticancer therapy, whichever occurs first. After this safety follow-up visit occurs, for patients who receive tisagenlecleucel concomitant medication collection will be modified as outlined in [Section 16.3](#) Appendix 3 and CRF Completion Guidelines (CCGs). Patients who do not receive tisagenlecleucel do not require reporting of concomitant medications after the safety follow-up visit. Modified collection of concomitant medication information during these periods is designed to capture tisagenlecleucel -related toxicity, severity, interventions and response/resolution following intervention. Any additions, deletions, or changes of these medications will be documented.

Medications, procedures and significant non-drug therapies (including physical therapy and blood transfusions) administered within 30 days prior to the patient signing ICF must be recorded on the appropriate Case Report Forms, as required by the modified reporting criteria in [Section 16.3](#) Appendix 3.

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication. If in doubt the investigator should contact the Novartis medical monitor before randomizing a subject or allowing a new medication to be started. If the subject is already enrolled, contact Novartis to determine if the subject should continue participation in the study.

6.2.2 Prohibited concomitant medication and non-drug therapy

The subject must be asked to notify the investigational site about any new medications he/she takes after the start of the study drug. All medications (other than study drug) and significant non-drug therapies (including physical therapy, herbal/natural medications and blood transfusions) administered during the study must be listed on the appropriate CRFs. For medication restrictions before leukapheresis, please refer to the recent [\[Investigational Leukapheresis, Cryopreservation and Scheduling Manual\]](#).

Medication restrictions before tisagenlecleucel infusion are specified below:

1. **Steroids:** Therapeutic doses of steroids must be stopped >72 hours or 5 half-lives, whichever is greater, prior to tisagenlecleucel infusion. However, the following physiological replacement doses of steroids are allowed: ≤40 mg/day hydrocortisone or equivalent

2. **Steroids or other immunosuppressant drugs** should NOT be used as pre-medication for tisagenlecleucel therapy (refer to [Section 6.1.3](#)) or following tisagenlecleucel infusion, except as required for physiological glucocorticoid replacement therapy, or under life threatening circumstances. Use of steroids with blood product administration should be eliminated just prior to and following tisagenlecleucel if possible or at least minimized.
3. **Antibody use** including anti-CD20 therapy (e.g., rituximab) should not be used within 4 weeks prior to tisagenlecleucel infusion.
4. **CNS disease prophylaxis or intrathecal therapy** must be stopped > 1 week prior to tisagenlecleucel infusion (e.g. intrathecal methotrexate)
5. **Radiation therapy** must be stopped >2 weeks prior to tisagenlecleucel infusion
6. **Investigational therapies** must not be used at any time while on study until the first progression following tisagenlecleucel infusion
7. **Live vaccines** must not be used in tisagenlecleucel recipients for at least 2 weeks prior to lymphodepletion and during tisagenlecleucel treatment until immune recovery
8. **Granulocyte macrophage-colony stimulating factor (GM-CSF)** should be avoided due to its potential to worsen CRS symptoms. Short acting granulocyte colony stimulating factor (G-CSF) should not be given within 72 hours of tisagenlecleucel infusion and long acting G-CSF should not be given within 10 days of tisagenlecleucel infusion.
9. **Anti-proliferative therapies**, other than lymphodepletion, including low dose daily or weekly maintenance chemotherapy should not be used within 2 weeks prior to infusion.
10. **Short acting drugs** used to treat primary disease (e.g. hydroxyurea, tyrosine kinase inhibitors, lenalidomide, ibrutinib) must be stopped > 72 hours prior to tisagenlecleucel

6.3 Subject numbering, treatment assignment, randomization

6.3.1 Subject numbering

Each subject is identified in the study by a Subject Number (Subject No.), that is assigned when the subject is first enrolled for screening and is retained as the primary identifier for the subject throughout his/her entire participation in the trial. The Subject No. consists of the Center Number (Center No.) (as assigned by Novartis to the investigative site) with a sequential subject number suffixed to it, so that each subject is numbered uniquely across the entire database. Upon signing the informed consent form, the subject is assigned to the next sequential Subject No. available.

The investigator or designated staff will contact the IRT and provide the requested identifying information for the subject to register them into the IRT. Once assigned, the Subject No. must not be reused for any other subject and the Subject No. for that individual must not be changed, even if the subject is re-screened. If the subject fails to start treatment for any reason, the reason will be entered into the appropriate CRF page.

6.3.2 Treatment assignment, randomization

The following methods have been used to minimize bias in treatment assignment. The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from subjects and investigator staff. A

subject randomization list will be produced by the IRT provider, or by a delegate under Novartis supervision, using a validated system that automates the random assignment of subject numbers to randomization numbers. These randomization numbers are linked to the different treatment arms.

Randomization will be stratified by remission duration (refractory or relapse <6 months from last dose of first line immunochemotherapy, relapsed 6 to 12 months from last dose of first line immunochemotherapy) and IPI (<2 v \geq 2). IPI will be assessed as follows as shown in [Table 6-1](#).

Table 6-1 **Defined risk factors and risk groups of International Prognostic Index (IPI)**

Risk Factors	
<ul style="list-style-type: none">• Age > 60 years• Performance Status 2 - 4• Tumor Stage III or IV• LDH > 1xULN• Extranodal lesions >1	
Number of Risk Factors	Risk Group
0-1	1 – low
2	2 – low intermediate
3	3 – high intermediate
4-5	4 – high

The randomization scheme for subjects will be reviewed and approved by a member of the Randomization Office.

6.4 Treatment blinding

Treatment will be open to subjects, investigator staff, persons performing the assessments, and the CTT.

6.5 Dose modification

Tisagenlecleucel is administered as a single dose and therefore dose modification is not applicable as subjects will receive a single intravenous (i.v.) infusion of $0.6 - 6.0 \times 10^8$ CAR-positive viable T cells.

For patients randomized to SOC therapy, dose modification may be made according to the local practice.

6.5.1 Follow-up for toxicities

For patients randomized to SOC the investigator should monitor any organ toxicities of SOC and take according measures as per local labeling and apply local standard of medical practice.

6.5.1.1 Follow up on potential drug-induced liver injury (DILI) cases

Patients with transaminase increase combined with total bilirubin (TBIL) increase may be indicative of potential drug induced liver injury (DILI), and should be considered as clinically important events.

The threshold for potential DILI may depend on the subject's baseline AST/ALT and TBIL value; subjects meeting any of the following criteria will require further follow-up as outlined below:

- For subjects with normal ALT and AST and TBIL value at baseline: AST or ALT $> 3.0 \times$ ULN combined with TBIL $> 2.0 \times$ ULN
- For subjects with elevated AST or ALT or TBIL value at baseline: [AST or ALT $> 2 \times$ baseline AND $> 3.0 \times$ ULN] OR [AST or ALT $> 8.0 \times$ ULN], combined with [TBIL $> 2 \times$ baseline AND $> 2.0 \times$ ULN]

Medical review needs to ensure that liver test elevations are not caused by cholestasis, defined as alkaline phosphatase (ALP) elevation $> 2.0 \times$ ULN with R value < 2 in subjects without bone metastasis, or elevation of ALP liver fraction in subjects with bone metastasis.

Note: (The R value is calculated by dividing the ALT by the ALP, using multiples of the ULN for both values. It denotes whether the relative pattern of ALT and/or ALP elevation is due to cholestatic ($R \leq 2$), hepatocellular ($R \geq 5$), or mixed ($R > 2$ and < 5) liver injury).

In the absence of cholestasis, these subjects should be immediately discontinued from study treatment, and repeat liver function test (LFT) as soon as possible, preferably within 48 hours from the awareness of the abnormal results. The evaluation should include laboratory tests, detailed history, physical assessment and the possibility of liver metastasis or new liver lesions, obstructions/compressions, etc.

1. Laboratory tests should include ALT, AST, albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, GGT, prothrombin time (PT)/international normalized ratio (INR) and alkaline phosphatase.
2. A detailed history, including relevant information, such as review of ethanol, concomitant medications, herbal remedies, supplement consumption, history of any pre-existing liver conditions or risk factors, should be collected.
3. Further testing for acute hepatitis A, B, C or E infection and liver imaging (e.g. biliary tract) may be warranted.
4. Obtain PK sample, as close as possible to last dose of, if PK analysis is performed in the study.
5. Additional testing for other hepatotropic viral infection (cytomegalovirus (CMV), EBV or herpes simplex virus (HSV), autoimmune hepatitis or liver biopsy may be considered as clinically indicated or after consultation with specialist/hepatologist.

All cases confirmed on repeat testing meeting the laboratory criteria defined above, with no other alternative cause for LFT abnormalities identified should be considered as “medically significant”, thus, met the definition of serious adverse event (SAE) and reported as SAE

using the term “potential drug-induced liver injury”. All events should be followed up with the outcome clearly documented

6.6 Additional treatment guidance

6.6.1 Treatment compliance

Novartis has established methods to ensure full traceability between the patient’s autologous leukapheresis and the tisagenlecleucel product in line with the requirements outlined in Regulation (EC) 1394/2007, the Directive 2004/23/EC as well as the rules and principles of the European Union (EU) “Detailed guidelines on good clinical practice (GCP) specific to advanced therapy medicinal Products” and 21 CFR 1271.250 and 21 CFR 1271.290. The data contributing to the full traceability of the cells are stored for a minimum of 30 years. Any product quality complaints are documented by the clinical site and reported to the Novartis Clinical Supplies Quality Assurance (QA) Department. A unique patient identifier will be used in order to maintain the chain of identity between the autologous leukapheresis product and the tisagenlecleucel batch and the link between patient identity and unique patient identifier will be confirmed prior to infusion. The investigational product handling manual provides an overview of how the company ensures that the cells which are procured, processed, stored, and distributed by or on behalf of the Novartis can be traced from leukapheresis to infusion.

The investigator or designee must maintain an accurate record of the drug receipt logs and Drug Accountability Forms. Drug accountability will be reviewed by the field monitor during site visits and prior to the completion of the study. At study close-out, and, as appropriate during the course of the study, the investigator will return a copy of the completed drug accountability forms to the Novartis monitor or to the Novartis address provided in the investigator folder at each site

6.6.1.1 Tisagenlecleucel compliance

As a single administration study, compliance will be assessed by the investigator and/or study personnel and captured in the Drug Accountability Form.

6.6.1.2 SOC compliance

For patients receiving SOC therapy either on Arm A as optional bridging to tisagenlecleucel treatment or Arm B as comparator arm treatment, local institutional guidelines should be followed to measure treatment compliance. Any dose interruptions or dose modifications should be documented on the appropriate eCRF.

6.6.2 Recommended treatment for adverse events

Subjects infused with tisagenlecleucel are at risk of developing a number of AE that are related either to tisagenlecleucel itself, other therapies (e.g. immunochemotherapy) and conditions concurrent with the subject’s primary disease. Following tisagenlecleucel infusion, subjects can be discharged from the treating site only if, in the investigator’s opinion, they do not demonstrate any adverse events or worsening of underlying diseases. This chapter describes the management of such AEs.

Drug and non-drug therapies used to treat AEs must be recorded on appropriate CRFs.

6.6.2.1 Cytokine Release Syndrome (CRS)

Ensure that tocilizumab is available on site prior to infusion of tisagenlecleucel. Supportive care, tocilizumab, and corticosteroids have been used for effective management of CRS. Prompt responses to tocilizumab have been seen in most subjects.

Identify cytokine release syndrome (CRS) based on clinical presentation (see [Section 4.6.1.1](#)). Evaluate for and treat other causes of fever, hypoxia, and hypotension. Although signs and symptoms of CRS occur in most cases within 1-14 days after tisagenlecleucel infusion, monitor patients for signs or symptoms of CRS for at least 4 weeks after treatment with tisagenlecleucel. Counsel patients to seek immediate medical attention should signs or symptoms of CRS occur at any time.

At the first sign of CRS, immediately evaluate patient for hospitalization and institute treatment with supportive care, tocilizumab and/or corticosteroids as indicated.

A detailed treatment algorithm for the management of CRS ([Lee et al 2014](#)) is presented below in [Table 6-2](#) and [Table 6-3](#). Subjects will be required to remain proximal to the treating site for the first 4 weeks.

Table 6-2 CRS management

CRS severity	Symptomatic treatment	Tocilizumab	Corticosteroids
Grade 1 Mild general symptoms requiring symptomatic treatment only e.g. fever, nausea, fatigue, headache, myalgia, malaise, etc.	After excluding other causes (e.g. infection), treat specific symptoms with e.g. antipyretics, anti-emetics, anti-analgesics, etc.	Not applicable	Not applicable
Grade 2 Symptoms requiring moderate intervention: Hypoxia requiring low-flow oxygen supplementation (<40%) or Hypotension requiring intravenous fluids and low dose of one vasopressor or Grade 2 organ toxicities	Oxygen supplementation Start intravenous fluids and, if no improvement, follow with a low-dose vasopressor Treat organ toxicities as per local guidelines	8 mg/kg intravenously (maximum 800 mg) over 1 hour. Repeat every 8 hours, if not responsive to intravenous fluids and increasing oxygen supplementation. Limit to 3 doses within 24 hours: maximum total of 4 doses.	If no improvement after 24 hours of treatment with tocilizumab, administer 1 mg/kg methylprednisolone intravenously twice daily (2 mg/kg as initial bolus can be given) or equivalent steroid dose. Continue until Grade 1 or less, then taper over 3 days
Grade 3 Symptoms requiring aggressive intervention: Hypoxia requiring high-flow oxygen supplementation (≥40%) or Hypotension requiring high-dose* or multiple vasopressors or Grade 3 organ toxicities or Grade 4 transaminitis	Oxygen supplementation Intravenous fluids and high-dosed vasopressor/s Treat organ toxicities as per local guidelines	See Grade 2	See Grade 2
Grade 4 Life-threatening symptoms requiring ventilator support, etc. or Grade 4 organ toxicity (excluding transaminitis)	Oxygen supplementation incl. ventilator support Intravenous fluids and high-dose* vasopressor/s Treat organ toxicities as per local guidelines	See Grade 2	Administer methylprednisolone 1000 mg intravenously daily (or equivalent steroid dose) for 3 days. If improves, then manage as per Grade 2.

*See [Table 6-3](#).

Table 6-3 High dose vasopressor use

Vasopressor	Dose to be given for ≥ 3 hours
Norepinephrine monotherapy	≥ 20 mcg/min
Dopamine monotherapy	≥ 10 mcg/kg/min
Phenylephrine monotherapy	≥ 200 mcg/min
Epinephrine monotherapy	≥ 10 mcg/min
If on vasopressin	Vasopressin + norepinephrine equivalent (NE) of ≥ 10 mcg/min*
If on combination vasopressors (not vasopressin)	NE of ≥ 20 mcg/min*

Vasopressin and Septic Shock Trial (VASST) Norepinephrine Equivalent Equation:

$$\text{NE dose} = [\text{norepinephrine (mcg/min)}] + [\text{dopamine (mcg/kg/min)} \div 2] + [\text{epinephrine (mcg/min)}] + [\text{phenylephrine (mcg/min)} \div 10]$$
[\(Lee et al 2014\)](#)

Other anti-cytokine therapies may also be considered upon their availability, if the patient does not respond to tocilizumab. If the patient experiences ongoing CRS despite administration of anti-cytokine directed therapies, anti-T-cell therapies such as cyclophosphamide, anti-thymocyte globulin (ATG) or alemtuzumab may be considered. These therapies need to be captured in appropriate CRFs.

The management of CRS is based solely upon clinical parameters as described in [Table 4-1](#). Ferritin, C-reactive protein (CRP) and serum cytokine levels should NOT be used for clinical management decisions. Cases of transient left ventricular dysfunction, as assessed by ECHO, have been reported in some patients with severe (Grade 4) CRS. Therefore consideration should be given to monitoring cardiac function by ECHO during severe CRS, especially in cases with prolonged severe hemodynamic instability, delayed response to high dose vasopressors, and/or severe fluid overload.

6.6.2.2 Neurologic adverse events

Neurologic events, primarily reflective of encephalopathy and delirium, may occur after tisagenlecleucel infusion. These present clinically as signs and symptoms of varying severity including: confusion, disorientation, agitation, aphasia, somnolence and tremors. In severe cases seizures, motor weakness, incontinence, impaired consciousness, increased intracranial pressure, and cerebral edema may be concurrent to, following the resolution or in the absence of CRS. Patients should be monitored for neurologic events, diagnostically worked-up and managed depending on the underlying pathophysiology and in accordance to local standard of care.

Evaluation:

- Thorough neurological examination, with frequent monitoring
- Diagnostic work up to evaluate potential secondary causes:
 - Brain imaging (CT scan and/or MRI): to exclude intracranial hemorrhage, disease relapse, evidence suggestive of infection or cerebral edema.
 - Lumbar puncture for CSF evaluation, if applicable.
 - Chemistry laboratory testing
 - Electroencephalography (EEG)

Management:

- If the neurological event is concurrent with CRS please refer to [Table 6-2](#). CRS algorithm table for treatment recommendation.
- Consider anti-seizure medications (e.g. Levetiracetam) for patient at high risk (prior history of seizure) or administer in the presence of seizure
- For encephalopathy, delirium or associated events: appropriate treatment and supportive care should be implemented as per local standard of care. In worsening events, consider a short course of steroids ([Neelapu et al 2018](#), [Teachey et al 2018](#))

6.6.2.3 Acute infusion reaction

Patients should be monitored for signs and symptoms of hypersensitivity following initiation of tisagenlecleucel infusion and treated appropriately. Tisagenlecleucel is contraindicated in patients with known hypersensitivity to tisagenlecleucel or to any component of the product formulation.

As appropriate, prophylactic medications should be administered to minimize the risk of immediate hypersensitivity including acute infusion reactions. It is recommended to pre-medicate all patients with acetaminophen (paracetamol) and diphenhydramine or another H1 antihistamine within approximately 30-60 minutes prior to tisagenlecleucel infusion. These medications can be repeated every 6 hours as needed. Non-steroidal anti-inflammatory medication may be prescribed for fever not responding to acetaminophen. Steroids should not be used for premedication. Systemic corticosteroids should only be used for severe conditions.

Should emergency treatment be required in the event of life-threatening hypersensitivity or other infusion-related reaction, supportive therapy such as oxygen and drug treatment should be given according to local institutional guidelines. Patients should be evaluated and carefully monitored until complete resolution of signs and symptoms.

6.6.2.4 Tumor lysis syndrome (TLS)

Patients should be closely monitored for signs and symptoms of TLS both before and after lymphodepleting chemotherapy and tisagenlecleucel infusion including relevant laboratory tests. To minimize risk of TLS, patients with elevated uric acid or high tumor burden should receive allopurinol, or an alternative prophylaxis, prior to tisagenlecleucel infusion. Events should be managed according to local guidelines.

Depending on the study phase, the following measures should be followed:

- Screening phase:
 - Prophylactic allopurinol, or a non-allopurinol alternative (e.g. febuxostat), and increased oral/ i.v. hydration prior to lymphodepleting chemotherapy and tisagenlecleucel infusion should be given in subjects with elevated uric acid or high tumor burden
 - Prompt supportive care in case of acute TLS (i.v. fluids and rasburicase as clinically indicated, when uric acid continues to rise despite allopurinol/febuxostat and fluids)
- Post-infusion monitoring phase:

- Frequent monitoring of the following laboratory tests (2 to 3 times/week for 3 weeks from start of lymphodepleting chemotherapy, then weekly): potassium, phosphorus, calcium, creatinine, and uric acid
- Encourage oral hydration

Based on laboratory and clinical TLS criteria (modified from [Cairo and Bishop \(2004\)](#)), the following measures for TLS should be also followed:

Laboratory TLS

Laboratory TLS is defined as two or more of the following values within three days before or in the days following tisagenlecleucel infusion:

- Uric acid ≥ 8 mg/dL or 25% increase from baseline
- Potassium ≥ 6 mEq/L or 25% increase from baseline
- Phosphorus ≥ 6.5 mg/dL (children) or ≥ 4.5 mg/dL (adults) or 25% increase from baseline
- Calcium ≤ 7 mg/dL or 25% decrease from baseline

Regimen:

If none or one of the laboratory values above is abnormal, continue to manage with allopurinol or a non-allopurinol alternative (e.g. febuxostat) and oral fluids. If uric acid remains elevated, consider i.v. fluids, rasburicase, and hospital monitoring.

Laboratory TLS should be managed with i.v. fluids, laboratory blood tests every 6 to 8 hours and inpatient care. Cardiac monitoring and rasburicase should be considered if uric acid remain elevated.

Clinical TLS

- Defined as the presence of laboratory TLS and ≥ 1 of the following criteria that cannot be explained by other causes:
- Serum creatinine ≥ 1.5 times the upper limit of the age-adjusted normal range
- Symptomatic hypocalcemia
- Cardiac arrhythmia

Clinical TLS should be managed with i.v. fluids, laboratory blood tests every 6 to 8 hours, cardiac monitoring, rasburicase/allopurinol/febuxostat and inpatient care (consider ICU).

6.6.2.5 Infections

Patients with active, uncontrolled infection should not start tisagenlecleucel treatment until the infection is resolved.

Patients should be monitored for signs and symptoms of infection and treated appropriately. As appropriate, prophylactic antibiotics should be administered and surveillance testing prior to and during treatment with tisagenlecleucel should be employed.

Institutional guidelines for vaccination (e.g. pneumococcus) should be followed before starting tisagenlecleucel therapy. As the lack of effective B cells after infusion makes the likelihood of a systemic infection considerable, vaccination with live virus vaccines should

not be given for at least 2 weeks prior to the start of lymphodepleting chemotherapy, during tisagenlecleucel and until immune recovery following treatment with tisagenlecleucel.

Any suspected cases of viral hepatitis or HIV should be referred to a specialist.

In patients with low immunoglobulin levels preventive measures such as immunoglobulin replacement and rapid attention to signs and symptoms of infection should be implemented as per age and local specific guidelines.

6.6.2.6 Febrile neutropenia

Febrile neutropenia (significantly decreased neutrophil count with fever) may develop in the course of chemotherapy (including lymphodepletion) and may be concurrent with CRS. A febrile subject should be evaluated for infection ([Section 4.6.1.5](#)) and CRS ([Section 4.6.1.1](#)) and managed appropriately with fluids, antibiotics, and supportive care, if applicable.

In the event that the patient develops sepsis or systemic bacteremia following tisagenlecleucel cell infusion, appropriate cultures and medical management should be initiated. If a contaminated tisagenlecleucel cell product is suspected, the product can be retested for sterility using archived samples that are stored at the manufacturing site.

6.6.2.7 B cell depletion and/ or hypogammaglobulinemia

Monitor immunoglobulin levels after treatment with tisagenlecleucel, use infection precautions including antibiotic prophylaxis and immunoglobulin replacement as appropriate and per local standard of care.

In case of new or worsening symptoms suggestive of PML, consultation with a neurologist should be considered.

6.6.2.8 Hematopoietic cytopenias lasting greater than or equal to 28 days

Myeloid growth factors are not recommended until CRS has been resolved and typically not until 28 days following tisagenlecleucel infusion. Haematopoietic cytopenias should be managed with standard measures of observation, blood product support growth factors and/or antibiotics as indicated and per local standard of care.

6.6.2.9 Replication competent lentivirus (RCL) production

If a positive RCL assay result is obtained from a subject blood specimen, (e.g., as detected by Vesicular Stomatitis Virus/Glycoprotein (VSV-G) quantitative PCR), the Investigator will be informed and the subject rescheduled for a retest of the DNA test. The subject must be isolated until an understanding of how to manage the subject becomes clear. Some considerations are:

- Intensive follow-up of the subject in consultation with gene therapy experts, study investigators, and Health Authorities
- Inform local and country specific public health officials
- Identify sexual partners and provide appropriate counseling and intervention

6.6.2.10 New or secondary malignancies including vector insertion site oligo/monoclonality)

If uncontrolled T cell proliferation occurs (e.g. expansion of T cells in the absence of CD19 antigen), subjects may be treated with corticosteroids such as methylprednisolone (2 mg/kg/d i.v.) or chemotherapy, such as high dose cyclophosphamide. Investigators should further discuss this with the sponsor. Toxicity associated with allogeneic or autologous T cell infusions has been managed with a course of pharmacologic immunosuppression. T cell associated toxicity has been reported to respond to systemic corticosteroids ([Lamers et al 2006](#)).

This theoretical toxicity is distinct from the toxicity associated with a CRS that develops during T cell proliferation upon exposure to CD19 expressing cells. CRS associated with T cell expansion is managed with anti-cytokine therapy, not immunosuppressants.

6.6.2.11 Graft versus host disease (GVHD)

GVHD can be severe but can be controlled with steroids and other immunosuppressants as per local standard of care.

6.7 Preparation and dispensation

For further preparation and administration of tisagenlecleucel, please refer to the [\[Investigational Product Handling Manual\]](#).

SOC immunochemotherapy should be handled as per local institutional guidance.

6.7.1 Handling of study treatment and additional treatment

6.7.1.1 Handling of study treatment

Study treatment must be received by a designated person at the study site, handled and stored safely and properly and kept in a secured location to which only the investigator and designated site personnel have access. Upon receipt, all study treatment must be stored according to the instructions specified on the labels and in the [Tisagenlecleucel Investigator's Brochure]. Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis CO Quality Assurance.

For more details please refer to [\[Investigational Product Handling Manual\]](#).

Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the study treatment but no information about the subject except for the medication number.

The investigator must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Monitoring of drug accountability will be performed by monitors during site visits or remotely and at the completion of the trial.

At the conclusion of the study, and as appropriate during the course of the study, the investigator will return all unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

Please refer to the recent [\[Investigational Product Handling Manual\]](#).

6.7.1.2 Handling of additional (SOC) treatment

SOC therapy should be handled and stored according to local guidelines.

7 Informed consent procedures

Eligible subjects may only be included in the study after providing (witnessed, where required by law or regulation), Institutional Review Board (IRB)/Independent Ethics Committee (IEC)-approved informed consent.

If applicable, in cases where the patient's representative(s) gives consent (if allowed according to local requirements), the patient must be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she must indicate agreement by personally signing and dating the written informed consent document.

Informed consent must be obtained before conducting any study-specific procedures (e.g. all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the subject source documents.

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the International Council on Harmonization (ICH) GCP guidelines and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed by Novartis before submission to the IRB/IEC.

Information about common side effects already known about the investigational drug can be found in the Investigator's Brochure (IB) and the core data sheet (CDS) for marketed drugs. This information will be included in the subject informed consent and should be discussed with the subject during the study as needed. Any new information regarding the safety profile of the investigational drug that is identified between IB updates will be communicated as appropriate, for example, via an investigator notification (IN) or an aggregate safety finding. New information might require an update to the informed consent and then must be discussed with the subject.

Women of child bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirements.

Male subjects must be informed that if a female partner becomes pregnant while he is enrolled in the study, contact with the female partner will be attempted to request her consent to collect pregnancy outcome information.

A copy of the approved version of all consent forms must be provided to Novartis/sponsor after IRB/IEC approval.

8 Visit schedule and assessments

Four tables will be used to manage assessments for the entire study duration

- Visit evaluation schedule from pre-screening to randomization ([Table 8-1](#))
- Visit evaluation schedule for Arm A ([Table 8-2](#))
- Visit evaluation schedule for Arm B ([Table 8-3](#))
- Visit evaluation schedule for patient who cross over from Arm B to Arm A ([Table 8-4](#))

Subjects should be seen for all visits/assessments as outlined in the assessment schedule or as close to the designated day/time as possible.

During the 1st month following tisagenlecleucel infusion, patients will undergo assessments as per [Table 8-2](#) or [Table 8-4](#). Visits denoted with an asterisk should be completed based on the timing of tisagenlecleucel infusion. For example, if tisagenlecleucel is infused on Day 40 rather than Day 28, then the Day 29 visit should take place on Day 41 and so forth.

Missed or rescheduled visits should not lead to automatic discontinuation. Subjects who prematurely discontinue the study for any reason should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the final visit will be performed. At this final visit, all dispensed investigational product should be reconciled, and the adverse event and concomitant medications recorded on the CRF.

Patients who received tisagenlecleucel and who discontinue early from the study due to BIRC-confirmed PD/SD prior to Month 60 will be followed every 3 months until month 12, then every 6 months until month 24, then yearly until month 60 in order to collect key safety data up to 5 years as part of long term additional follow-up. In cases where a patient discontinues without BIRC confirmed PD/SD, it may be possible for the patient to be followed for key safety follow-up only after consultation and documented agreement with the Novartis medical monitor.

After 5 years, the patients will continue to be followed for safety in a separate long-term follow-up long term follow-up (LTFU) study, [CTL019A2205B].

In each table, required assessments are indicated with an “X” at the visits when they are performed. The letter (D) under the category column indicates the assessments that will have data entered into the clinical database and (S) is for assessments that will have data remain as source documentation. All data obtained from these assessments must be supported in the patient’s source documentation.

No CRF will be used in the patient’s source documentation.

Table 8-1 Visit evaluation schedule pre-screening to randomization

Phase: Screening to Randomization	Category	Protocol Section	Pre-Screening	Screening	Randomization
Visit					
Study day				D-14 to -1 (± 7d)	Day 1
Identify Patient	S	8.1.	X		
Confirm Slot Availability	S	8.1.	X		
Obtain Informed Consent	D	7.		X	
IRT Registration	S	6.3.1.		X	X
Randomization by IRT	D	6.3.2.			X
Stratification by IRT	D	6.3.2.			X
Demography	D	8.2.		X	
Inclusion/exclusion criteria	D	5.		X	
Medical history	D	8.2.		X	
Diagnosis and Extent of Cancer	D	8.2.		X	
Prior antineoplastic therapy	D	16.3.		X	
Prior/concomitant medications	D	6.2.1.		X	X
Tumor Biopsy (CD19, tumor subtype, gene expression, PD1, PD-L1, Ki67, t(14;18), bcl-2, bcl-6, c-myc)	D	8.4.1.		X	
Physical examination	S	8.4.		X	
Performance status	D	8.4.		X	
Prognostic score (IPI)	D	6.3.2.		X	
Height	D	8.4.		X	
Weight	D	8.4.		X	
Vital signs	D	8.4.		X	
Pulse oximetry	D	8.4.		X	
Spirometry	D	8.4.4.		X	
ECHO/MRA	D	8.4.2.1.		X	
Electrocardiogram (ECG)	D	8.4.2.		X	
Leukapheresis	D	8.1.		X	
PET-CT with contrast enhanced diagnostic (Dx) CT – Neck, Chest, Abdomen, Pelvis,	D	8.3.		X (allowed up to 4 weeks prior to randomization)	
CT/MRI – Neck, Chest, Abdomen, Pelvis	D	8.3.		X If no Dx PET-CT	
Dedicated FDG-PET	D	8.3.		X If no PET-CT	
CT/MRI Brain	D	8.3.		As clinically indicated	
Response evaluation per Lugano classification 2014	D	16.2.		X	
Bone marrow biopsy and/ or aspirate	D	8.3.		X (allowed up to 4 weeks prior to randomization)	
CSF cytology by Lumbar puncture	D	8.3.		X (allowed up to 4 weeks prior to randomization)	

Phase: Screening to Randomization	Category	Protocol Section	Pre-Screening	Screening	Randomization
Visit					
Study day				D-14 to -1 (± 7d)	Day 1
Adverse events	D	10.1.1.		X	X
Pregnancy Reporting	S	10.1.4.			X
Central Hematology	D	8.4.1.		X	
Central Chemistry	D	8.4.1.		X	
Central Cardiac Enzymes	D	8.4.1.		X	
Flow cytometry before leukapheresis (PB)	D	8.5.2.		X	
Flow cytometry (leukapheresis product)	D	8.4.1.		X	
Serum or Urine pregnancy test	D	8.4.1.		X (Serum)	X (Serum)
Viral serology (EBV, HIV, HBsAg, HBsAb HBcAb, HCVab)	D	8.4.1.		X	
Central Coagulation (PT, aPTT, INR, fibrinogen, D-dimer)	D	8.4.1.		X	
Central Serum immunoglobulin levels (IgG, IgA, IgM)	D	8.4.1.		X	
Urine Dipstick	D	8.4.1.		X	
Cytokines (serum)	D	8.5.2.			X
Tisagenlecleucel cellular kinetics by qPCR (PB)	D	8.5.2.			X
Tisagenlecleucel cellular kinetics by flow cytometry (PB)	D	8.5.2.			X
Immunogenicity (serum)	D	8.5.2.			X
Immunogenicity (Peripheral Blood)	D	8.5.2.			X
Tisagenlecleucel cellular kinetics – Bone Marrow (qPCR)	D	8.5.2.			X (pre-dose)
Tisagenlecleucel cellular kinetics – Bone Marrow (flow cytometry)	D	8.5.2.			X (pre-dose)
Peripheral Blood (immuno-phenotyping, Ig deep sequencing, gene expression)	D	8.5.3.			X
Peripheral blood (cell levels-central assessment)	D	8.5.3.			X
RCL by VSV-g q-PCR	D	8.4.4.			X
Leukapheresis sample for correlative studies	D	8.5.3.		X	
SF-36v2 (Acute Form)	D	8.5.			X
FACT-Lym	D	8.5.			X
EQ-5D-5L	D	8.5.			X
Healthcare resource utilization	D	8.5.			X
Disposition (End of Phase)	D	8.1.1.			X

Table 8-2 Visit evaluation schedule for Arm A (patients randomized to tisagenlecleucel treatment strategy)

Phase Arm A						Tisagenlecleucel Treatment and Follow up																		
Visit	Category	Protocol Section	Optional Bridging Chemotherapy	Lymphodepleting Chemotherapy	Pre-tisagenlecleucel Infusion	Tisagenlecleucel Infusion	Post-tisagenlecleucel infusion (*See Section 8 for additional details regarding the timing of these visits)														End of Treatment and Primary Follow-up	Safety Follow-up Visit ¹	Long term additional Follow-up ²	Survival Follow-up
Study day			D1-D21±7d	D22 to D25* (inf-6 to inf-3	D27* (inf-1)	D28* (inf)	D29* (inf + 1)	D31* (inf+3) ±1d	D34* (inf+6) ±1d	D38* (inf+10) ±3d	D41* (inf+13) ±3d	Week 6±7d	D49* (inf+21)±3d	Week 8* (inf+28)± 7d	Week 12 ±7d	M4 M5, ±14d	M6 M9 M12 ±14d	M18 ±14d	M24 M36 M48 ±14d	M60±14d	See footnote ¹	Post relapse ²	q3M	
IRT Registration	S		X	X		X						X			X					X				
Patient History																								
Concomitant medications	D	16.3.	Continuous until 8 weeks after last treatment administration or prior to start of new anticancer therapy, whichever comes first																		X			
Concomitant medications (modified captured)	D	16.3.													For patients that receive tisagenlecleucel, starting 8 weeks after tisagenlecleucel or prior to start of new anticancer therapy, whichever comes first							X		
Antineoplastic therapies after tisagenlecleucel infusion	D	16.3.					Continuous															X	X	
Physical Assessments																								
Physical examination	S	8.4.	X		X	X	X	X		X		X												

Phase Arm A					Tisagenlecleucel Treatment and Follow up																			
Visit	Category	Protocol Section	Optional Bridging Chemotherapy	Lymphodepleting Chemotherapy	Pre-tisagenlecleucel Infusion	Tisagenlecleucel Infusion	Post-tisagenlecleucel infusion (*See Section 8 for additional details regarding the timing of these visits)													End of Treatment and Primary Follow-up	Safety Follow-up Visit ¹	Long term additional Follow-up ²	Survival Follow-up	
Study day			D1-D21±7d	D22 to D25* (inf-6 to inf-3	D27* (inf-1)	D28* (inf)	D29*(inf + 1)	D31*(inf+3) ±1d	D34*(inf+6) ±1d	D38*(inf+10) ±3d	D41*(inf+13) ±3d	Week 6±7d	D49*(inf+21)±3d	Week 8* (inf+28)± 7d	Week 12 ±7d	M4 M5, ±14d	M6 M9 M12 ±14d	M18 ±14d	M24 M36 M48 ±14d	M60±14d	See footnote ¹	Post relapse ²	q3M	
Performance status	D	8.4.	X q2w		X	X	X	X		X			X	X	X	X	X	X	X	X	X			
Weight	D	8.4.	X	X		X								X	X	X	X	X	X	X	X			
Vital signs	D	8.4.	X q2w		X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X			
Pulse oximetry	D	8.4.				X	X	X	X	X	X		X	X	X	X	X	X	X	X	X			
ECG	D	8.4.2.				X	as clinically indicated																	
Intervention																								
Lymphodepleting chemotherapy	D	6.1.4.		X																				
Tisagenlecleucel infusion prerequisite assessment	S	6.1.1.				X																		
Tisagenlecleucel infusion	D	6.1.1.				X																		
Efficacy Assessments																								
PET-CT with contrast enhanced diagnostic (Dx) CT – Neck, Chest, Abdomen, Pelvis	D	8.3.													X		X M6 only							

Phase Arm A						Tisagenlecleucel Treatment and Follow up																		
Visit	Category	Protocol Section	Optional Bridging Chemotherapy	Lymphodepleting Chemotherapy	Pre-tisagenlecleucel Infusion	Tisagenlecleucel Infusion	Post-tisagenlecleucel infusion (*See Section 8 for additional details regarding the timing of these visits)														End of Treatment and Primary Follow-up	Safety Follow-up Visit ¹	Long term additional Follow-up ²	Survival Follow-up
Study day			D1-D21±7d	D22 to D25* (inf-6 to inf-3	D27* (inf-1)	D28* (inf)	D29*(inf + 1)	D31*(inf+3) ±1d	D34*(inf+6) ±1d	D38*(inf+10) ±3d	D41*(inf+13) ±3d	Week 6±7d	D49*(inf+21)±3d	Week 8* (inf+28)± 7d	Week 12 ±7d	M4 M5, ±14d	M6 M9 M12 ±14d	M18 ±14d	M24 M36 M48 ±14d	M60±14d	See footnote ¹	Post relapse ²	q3M	
CT/MRI – Neck, Chest, Abdomen, Pelvis (PET-CT with Dx CT is preferred for all image visits)	D	8.3.										X			X if no Dx PET-CT		X if no Dx PET-CT	X	X	X				
Dedicated FDG-PET	D	8.3.													X if no PET-CT		M6 only if no PET-CT							
Response evaluation per Lugano classification 2014	D	16.2.										X			X		X	X	X	X				
Response (CR) confirmation by PET-CT or dedicated FDG-PET	D	8.3.					Only for new CR and not previously documented																	
Bone marrow biopsy and/or aspirate for efficacy	D	8.3.										Only if prior history of BM involvement to confirm CR												
CT/MRI Brain	D	8.3.						As clinically indicated																

Phase Arm A					Tisagenlecleucel Treatment and Follow up																					
Visit	Category	Protocol Section	Optional Bridging Chemotherapy	Lymphodepleting Chemotherapy	Pre-tisagenlecleucel Infusion	Tisagenlecleucel Infusion	Post-tisagenlecleucel infusion (*See Section 8 for additional details regarding the timing of these visits)														End of Treatment and Primary Follow-up	Safety Follow-up Visit ¹	Long term additional Follow-up ²	Survival Follow-up		
Study day			D1-D21±7d	D22 to D25* (inf-6 to inf-3	D27* (inf-1)	D28* (inf)	D29*(inf + 1)	D31*(inf+3) ±1d	D34*(inf+6) ±1d	D38*(inf+10) ±3d	D41*(inf+13) ±3d	Week 6±7d	D49*(inf+21)±3d	Week 8* (inf+28)± 7d	Week 12 ±7d	M4 M5, ±14d	M6 M9 M12 ±14d	M18 ±14d	M24 M36 M48 ±14d	M60±14d	See footnote ¹	Post relapse ²	q3M			
CSF cytology by Lumbar puncture	D	8.3.							As clinically indicated																	
Safety assessments																										
Adverse events	D	10.1.	Continuous until 8 weeks after tisagenlecleucel or prior to start of new anticancer therapy, whichever comes first																			X				
Protocol defined AE and AESI, including new malignancies	D	16.2.											Continuous starting 8 weeks after tisagenlecleucel or prior to start of new anticancer therapy, whichever comes first								X	X				
Pregnancy Reporting	S	10.1.4.	Continuous																			X	X			
Laboratory assessments																										
Central Hematology	D	8.4.1.		X		X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X				
Central Chemistry	D	8.4.1.		X		X	X	X	X	X		X	X	X	X	X	X	X	X	X	X					
Central Cardiac Enzymes	D	8.4.1.		X				X				X	X	X	X	X	X	X	X	X						

Phase Arm A						Tisagenlecleucel Treatment and Follow up																			
Visit	Category	Protocol Section	Optional Bridging Chemotherapy	Lymphodepleting Chemotherapy	Pre-tisagenlecleucel Infusion	Tisagenlecleucel Infusion	Post-tisagenlecleucel infusion (*See Section 8 for additional details regarding the timing of these visits)															End of Treatment and Primary Follow-up	Safety Follow-up Visit ¹	Long term additional Follow-up ²	Survival Follow-up
Study day			D1-D21±7d	D22 to D25* (inf-6 to inf-3	D27* (inf-1)	D28* (inf)	D29*(inf + 1)	D31*(inf+3) ±1d	D34*(inf+6) ±1d	D38*(inf+10) ±3d	D41*(inf+13) ±3d	Week 6±7d	D49*(inf+21)±3d	Week 8* (inf+28)± 7d	Week 12 ±7d	M4 M5, ±14d	M6 M9 M12 ±14d	M18 ±14d	M24 M36 M48 ±14d	M60±14d	See footnote ¹	Post relapse ²	q3M		
Serum or Urine pregnancy test	S	8.4.1.	X serum	X serum	X serum						X		X	X	X	X	X (monthly testing between visits, M60/EOS visit must be serum testing)				X	X			
Central Coagulation (PT, aPTT, INR, fibrinogen, D-dimer)	D	8.4.1.				X			X		X			X	X	X					X				
Central Serum immunoglobulin levels (IgG, IgA, IgM)	D	8.4.1.									X			X	X	X	X								
Rapid Influenza (A and B) Testing	D	8.4.1.		Within 10d to planned infusion																					
Urine Dipstick	D	8.4.1.	X	X			X																		
Tisagenlecleucel cellular kinetics, biomarker and safety assessments																									
Cytokines (serum)	D	8.5.2.		X	X		X	X	X	X	X		X	X	X		M6 and M12								

Phase Arm A						Tisagenlecleucel Treatment and Follow up																			
Visit	Category	Protocol Section	Optional Bridging Chemotherapy	Lymphodepleting Chemotherapy	Pre-tisagenlecleucel Infusion	Tisagenlecleucel Infusion	Post-tisagenlecleucel infusion (*See Section 8 for additional details regarding the timing of these visits)														End of Treatment and Primary Follow-up	Safety Follow-up Visit ¹	Long term additional Follow-up ²	Survival Follow-up	
Study day			D1-D21±7d	D22 to D25* (inf-6 to inf-3	D27* (inf-1)	D28* (inf)	D29*(inf + 1)	D31*(inf+3) ±1d	D34*(inf+6) ±1d	D38*(inf+10) ±3d	D41*(inf+13) ±3d	Week 6±7d	D49*(inf+21)±3d	Week 8* (inf+28)± 7d	Week 12 ±7d	M4 M5, ±14d	M6 M9 M12 ±14d	M18 ±14d	M24 M36 M48 ±14d	M60±14d	See footnote ¹	Post relapse ²	q3M		
Immunogenicity (serum)	D	8.5.2.			X						X			X		X M4 only	M6 and M12	X	M24 only	X					
Immunogenicity (Peripheral Blood)	D	8.5.2.			X						X			X		X M4 only	M6 and M12	X	M24 only	X		X			
Rituximab PK	D	8.5.2.			X					X						X M4 only									
CRS assessments in peripheral blood (serum cytokines, inflammatory markers, tisagenlecleucel cellular kinetics)	D	8.5.2.						As clinically indicated depending upon the presence and time- course of CRS and administration of anti-cytokine therapies – refer to Table 8-18 , Table 8-19 : For tisagenlecleucel cellular kinetics, refer to Table 8-11 (qPCR in peripheral blood) and Table 8-12 (flow in peripheral blood). For biomarkers refer to Table 8-20 .																	

Phase Arm A						Tisagenlecleucel Treatment and Follow up																			
Visit	Category	Protocol Section	Optional Bridging Chemotherapy	Lymphodepleting Chemotherapy	Pre-tisagenlecleucel Infusion	Tisagenlecleucel Infusion	Post-tisagenlecleucel infusion (*See Section 8 for additional details regarding the timing of these visits)															End of Treatment and Primary Follow-up	Safety Follow-up Visit ¹	Long term additional Follow-up ²	Survival Follow-up
Study day			D1-D21±7d	D22 to D25* (inf-6 to inf-3	D27* (inf-1)	D28* (inf)	D29*(inf + 1)	D31*(inf+3) ±1d	D34*(inf+6) ±1d	D38*(inf+10) ±3d	D41*(inf+13) ±3d	Week 6±7d	D49*(inf+21)±3d	Week 8* (inf+28)± 7d	Week 12 ±7d	M4 M5, ±14d	M6 M9 M12 ±14d	M18 ±14d	M24 M36 M48 ±14d	M60±14d	See footnote ¹	Post relapse ²	q3M		
Tisagenlecleucel, cytokines, inflammatory markers and IL6R assessments in PB in patients treated with tocilizumab	D	8.5.2.						see (Table 8-18)																	
Tisagenlecleucel cellular kinetics by qPCR (PB)	D	8.5.2.		X		X	X	X	X	X			X	X	X	X M4 only	X	X	X	X	X		X	X	
Tisagenlecleucel cellular kinetics by flow cytometry (Peripheral Blood)	D	8.5.2.		X		X		X	X	X	X		X	X	X	X M4 only	X	X							
Tumor biopsy (CD19 expression, PD1, PDL1, IDO1, gene expression profiling)	D	8.5.3.																							
Tisagenlecleucel cellular kinetics Bone Marrow (qPCR)	D	8.5.2.												X		X M4 only	As clinically indicated								

Phase Arm A						Tisagenlecleucel Treatment and Follow up																		
Visit	Category	Protocol Section	Optional Bridging Chemotherapy	Lymphodepleting Chemotherapy	Pre-tisagenlecleucel Infusion	Tisagenlecleucel Infusion	Post-tisagenlecleucel infusion (*See Section 8 for additional details regarding the timing of these visits)														End of Treatment and Primary Follow-up	Safety Follow-up Visit ¹	Long term additional Follow-up ²	Survival Follow-up
Study day			D1-D21±7d	D22 to D25* (inf-6 to inf-3	D27* (inf-1)	D28* (inf)	D29*(inf + 1)	D31*(inf+3) ±1d	D34*(inf+6) ±1d	D38*(inf+10) ±3d	D41*(inf+13) ±3d	Week 6±7d	D49*(inf+21)±3d	Week 8* (inf+28)± 7d	Week 12 ±7d	M4 M5, ±14d	M6 M9 M12 ±14d	M18 ±14d	M24 M36 M48 ±14d	M60±14d	See footnote ¹	Post relapse ²	q3M	
Tisagenlecleucel cellular kinetics - Bone marrow (flow cytometry)	D	8.5.2.												X		X M4 only	As clinically indicated							
Immunophenotyping, Ig deep sequencing, gene expression- Peripheral Blood	D	8.5.3.		X	X				X	X				X	X		X	X	X	X			X	
Peripheral blood (B and T cell levels- central assessment)	D	8.5.3.		X	X				X	X	X				X		M6 and M12	X	X	X		X		
RCL by VSV-g q- PCR	D	8.4.5.		X											X		X	X	X	X		X		
Tisagenlecleucel cell product sample for correlative studies	D	8.5.3.		X																				
Electronic Patient Reported Outcomes																								
SF-36v2 (Acute Form)	D	8.5.1.1.										X		X	X		X	X	X	X ³		X ³		
EQ-5D-5L	D	8.5.1.3.										X		X	X		X	X	X	X ³		X ³		
FACT-Lym	D	8.5.1.2.										X		X	X		X	X	X	X ³		X ³		

Phase Arm A						Tisagenlecleucel Treatment and Follow up																	
Visit	Category	Protocol Section	Optional Bridging Chemotherapy	Lymphodepleting Chemotherapy	Pre-tisagenlecleucel Infusion	Tisagenlecleucel Infusion	Post-tisagenlecleucel infusion (*See Section 8 for additional details regarding the timing of these visits)													End of Treatment and Primary Follow-up	Safety Follow-up Visit ¹	Long term additional Follow-up ²	Survival Follow-up
Study day			D1-D21±7d	D22 to D25* (inf-6 to inf-3	D27* (inf-1)	D28* (inf)	D29*(inf + 1)	D31*(inf+3) ±1d	D34*(inf+6) ±1d	D38*(inf+10) ±3d	D41*(inf+13) ±3d	Week 6±7d	D49*(inf+21)±3d	Week 8* (inf+28)± 7d	Week 12 ±7d	M4 M5, ±14d	M6 M9 M12 ±14d	M18 ±14d	M24 M36 M48 ±14d	M60±14d	See footnote ¹	Post relapse ²	q3M
Healthcare resource utilization	D	8.5.1.4.	Continuous until Month 6																				
Survival Follow-up	D	9.2.	For all randomized patients, follow-up for survival every 3 months until the end of study (defined as the last visit for the last patient randomized). If a patient misses a quarterly scheduled visit where survival status is required, or if the time-point does not align with a scheduled visit, survival status can be obtained via phone contact																				
Disposition (End of Phase)	D	9.1.2.																		X		X	
1 The safety follow-up visit should occur 8 weeks after last treatment administration or prior to starting new anticancer therapy, whichever occurs first. After this safety visit occurs, adverse events and concomitant medications will follow-up a modified reporting criteria in patients that receive tisagenlecleucel (Section 16.3 Appendix 3).																							
2 Patients that receive tisagenlecleucel and have BIRC-confirmed PD/SD prior to Month 60 will be followed to collect key safety data every 3 months until M12, then every 6 months until M24, then yearly until M60. All visits may occur ±14 days.																							
3 Patients that experience BIRC-confirmed PD/SD prior to Month 60 should complete PROs at the end of treatment visit, 4 weeks after PD/SD ±7 days , 12 weeks after PD/SD ±14 days, and 6 months after PD/SD ±14 days. If these timepoints align with scheduled long term additional follow-up visits they may be completed at the same time.																							

Table 8-3 Visit evaluation schedule for Arm B (patients randomized to SOC treatment strategy)

Phase Arm B			Treatment and Follow up														
Visit	Category	Protocol Section	SOC - Month 1			SOC - Week 8		SOC- Week 12 to month 48					End of Treatment and Follow- up	Crossover	Safety Follow-up Visit ¹	Survival Follow- up	
Study day			D1	D14 ±1d	D28 ±3d	Week 6±7d	Week 8 ±7d	Week12 ±7d	M4 M5 ±14d	M6 M9 M12 ±14d	M18 ±14d	M24 M36 M48 ±14d	M60 ±14d	Week 12 ±7d onwards	See footnote ¹	q3M	
IRT Registration	S		X			X		X					X	X			
Concomitant medications	D	16.3.	Continuous until 8 weeks after the last dose of SOC study treatment or prior to start of other new anticancer therapy, whichever comes first												X	X	
Antineoplastic therapies	D	16.3.	Continuous													X	
Physical examination	S	8.4.	X	X	X	X	X	X	X	X	X	X	X	X			
Performance status	D	8.4.	X	X	X	X	X	X	X	X		X	X	X			
Weight	D	8.4.	X		X		X	X	X	X	X	X	X				
Vital signs	D	8.4.	X	X	X	X	X	X	X	X	X	X	X				
ECG	D	8.4.2.	As clinically indicated											X			
Chemotherapy	D	6.1.1.	SOC treatment at the investigator's discretion														
confirm patient eligibility for cross-over	D	8.3.3.												X			
PET-CT with contrast enhanced diagnostic (Dx) CT – Neck, Chest, Abdomen, Pelvis	D	8.3.						X		X M6 only							
CT/MRI – Neck, Chest, Abdomen, Pelvis	D	8.3.				X		X if no Dx PET-CT		X M6 only if no Dx PET-CT	X	X	X				

Phase Arm B			Treatment and Follow up													
Visit	Category	Protocol Section	SOC - Month 1			SOC - Week 8		SOC- Week 12 to month 48					End of Treatment and Follow- up	Crossover	Safety Follow-up Visit ¹	Survival Follow- up
Study day			D1	D14 ±1d	D28 ±3d	Week 6±7d	Week 8 ±7d	Week12 ±7d	M4 M5 ±14d	M6 M9 M12 ±14d	M18 ±14d	M24 M36 M48 ±14d	M60 ±14d	Week 12 ±7d onwards	See footnote ¹	q3M
Dedicated PET	D	8.3.						X if no PET-CT		M6 only if no PET-CT						
Response evaluation per Lugano classification 2014	D	16.2.				X		X		X	X	X	X	X		
Response (CR) confirmation by PET-CT or PET	D	8.3.	Only for new CR and not previously documented													
CT/MRI Brain	S	8.3.	As clinically indicated													
Bone marrow biopsy and/or aspirate	D	8.3.				Only if prior history of BM involvement to confirm CR on PET-CT or PET										
CSF cytology by Lumbar puncture	D	8.3.	As clinically indicated													
Adverse events	D	10.1.1.	Continuous until 8 weeks after the last dose of SOC study treatment or prior to start of other new anticancer therapy, whichever comes first												X	
Pregnancy Reporting	S	10.1.4.	Continuous												X	
Central Hematology	D	8.4.1.		X	X	X	X	X	X	X	X	X	X	X	X	
Central Chemistry	D	8.4.1.		X	X	X	X	X	X	X	X	X	X	X	X	
Central Cardiac Enzymes	D	8.4.1.		X	X	X	X	X	X	X	X	X	X	X		
Serum or Urine pregnancy test	S	8.4.1.	X	X	X	X	X	X	X	X (monthly testing between visits, M60/EOS visit must be serum testing)					X	

Phase Arm B			Treatment and Follow up														
Visit	Category	Protocol Section	SOC - Month 1			SOC - Week 8		SOC- Week 12 to month 48					End of Treatment and Follow- up	Crossover	Safety Follow-up Visit ¹	Survival Follow- up	
Study day			D1	D14 ±1d	D28 ±3d	Week 6±7d	Week 8 ±7d	Week12 ±7d	M4 M5 ±14d	M6 M9 M12 ±14d	M18 ±14d	M24 M36 M48 ±14d	M60 ±14d	Week 12 ±7d onwards	See footnote ¹	q3M	
Coagulation (PT, aPTT, INR, fibrinogen, D-dimer)	D	8.4.1.		X			X	X	X						X		
Serum immunoglobulin levels (IgG, IgA, IgM)	D	8.4.1.					X	X	X	X							
Urine Dipstick	D	8.4.1.	X	Repeat urinalysis following local labeling of SOC and local medical practice													
SF-36v2 (Acute Form)	D	8.5.1.2.				X	X	X		X	X	X	X ²	X			
EQ-5D-5L	D	8.5.1.2.				X	X	X		X	X	X	X ²	X			
FACT-Lym	D	8.5.1.2.				X	X	X		X	X	X	X ²	X			
Healthcare resource utilization	D	8.5.1.3.	Continuous until Month 6														
Survival follow-up	D	8.5.5.	For all randomized patients, follow-up for survival every 3 months until the end of study (defined as the last visit for the last patient randomized). If a patient misses a quarterly scheduled visit where survival status is required, or if the time-point does not align with a scheduled visit, survival status can be obtained via phone contact														
Disposition (End of Phase)	D	9.1.2.											X	X			
1 The safety follow-up visit should occur 8 weeks after last treatment administration or prior to starting new anticancer therapy, whichever occurs first. If the patient received ASCT, this would occur 8 weeks after ASCT. After this safety visit occurs, no new adverse events or concomitant medications need to be reported. 2 Patients that experience BIRC-confirmed PD/SD prior to Month 60, but do not plan to crossover, should complete PROs at the end of treatment visit, 4 weeks after PD/SD ±7 days , 12 weeks after PD/SD ±14 days, and 6 months after PD/SD ±14 days. Patients that plan to crossover should complete PROs at the crossover visit.																	

Table 8-4 Visit evaluation schedule for patients who cross over from Arm B (SOC) to Arm A (tisagenlecleucel)

Phase Crossover						Tisagenlecleucel Treatment and Follow up																		
Visit	Category	Protocol Section	Optional Bridging Chemo	Lymphodepleting Chemotherapy	Pre-tisagenlecleucel Infusion	Tisagenlecleucel Infusion	Post-tisagenlecleucel infusion (*See Section 8 for additional details regarding the timing of these visits)														End of Treatment and Primary Follow-up	Safety Follow-up ¹	Long term additional Follow-up ²	Survival Follow-up
Study day			D1-D21±7d	D22 to D25* (inf-6 to inf-3)	D27* (inf-1)	D28*(inf)	D29*(inf + 1)	D31*(inf+3) ±1d	D34*(inf+6) ±1d	D38*(inf+10) ±3d	D41*(inf+13) ±3d	Week 6±7d	D49*(inf+21)±3d	Week 8 (inf+28)±7d	Week 12 ±7d	M4 M5, ±14d	M6 M9 M12 ±14d	M18 ±14d	M24 M36 M48 ±14d	M60±14d	See footnote ¹	Post relapse ²	q3M	
IRT Registration	S		X	X		X						X			X					X				
Patient History																								
Concomitant medications	D	16.3.	Continuous until 8 weeks after last treatment administration or prior to start of new anticancer therapy, whichever comes first																		X			
Concomitant medications (modified captured)	D	16.3.													For patients that receive tisagenlecleucel, starting 8 weeks after tisagenlecleucel or prior to start of new anticancer therapy, whichever comes first						X			
Antineoplastic therapies after tisagenlecleucel infusion	D	16.3.					Continuous															X	X	
Physical Assessments																								
Physical examination	S	8.4.	X		X	X	X		X		X	X	X											
Performance status	D	8.4.	X		X	X	X		X		X	X	X	X	X	X	X	X	X	X				
Weight	D	8.4.	X	X		X								X	X	X	X	X	X	X				

Phase Crossover						Tisagenlecleucel Treatment and Follow up																		
Visit	Category	Protocol Section	Optional Bridging Chemo	Lymphodepleting Chemotherapy	Pre-tisagenlecleucel Infusion	Tisagenlecleucel Infusion	Post-tisagenlecleucel infusion (*See Section 8 for additional details regarding the timing of these visits)														End of Treatment and Primary Follow-up	Safety Follow-up ¹	Long term additional Follow-up ²	Survival Follow-up
Study day			D1-D21±7d	D22 to D25* (inf-6 to inf-3)	D27* (inf-1)	D28*(inf)	D29*(inf + 1)	D31*(inf+3) ±1d	D34*(inf+6) ±1d	D38*(inf+10) ±3d	D41*(inf+13) ±3d	Week 6±7d	D49*(inf+21)±3d	Week 8 (inf+28)±7d	Week 12 ±7d	M4 M5, ±14d	M6 M9 M12 ±14d	M18 ±14d	M24 M36 M48 ±14d	M60±14d	See footnote ¹	Post relapse ²	q3M	
Vital signs	D	8.4.	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Pulse oximetry	D	8.4.				X	X	X	X	X	X			X	X	X	X	X	X	X				
ECG	D	8.4.2.				X	as clinically indicated																	
Intervention																								
Lymphodepleting chemotherapy	D	6.1.4.		X																				
Tisagenlecleucel infusion prerequisite assessment	S	6.1.1.				X																		
Tisagenlecleucel infusion	D	6.1.1.				X																		
Efficacy Assessments																								
Response evaluation per Lugano classification 2014	D	16.2.										X			X		X	X	X	X				
Safety assessments																								
Adverse events	D	10.1.	Continuous until 8 weeks after last treatment administration or prior to start of new anticancer therapy, whichever comes first																			X		

Phase Crossover						Tisagenlecleucel Treatment and Follow up																			
Visit	Category	Protocol Section	Optional Bridging Chemo	Lymphodepleting Chemotherapy	Pre-tisagenlecleucel Infusion	Tisagenlecleucel Infusion	Post-tisagenlecleucel infusion (*See Section 8 for additional details regarding the timing of these visits)															End of Treatment and Primary Follow- up	Safety Follow-up ¹	Long term additional Follow-up ²	Survival Follow-up
Study day			D1-D21±7d	D22 to D25* (inf-6 to inf-3)	D27* (inf-1)	D28*(inf)	D29*(inf + 1)	D31*(inf+3) ±1d	D34*(inf+6) ±1d	D38*(inf+10) ±3d	D41*(inf+13) ±3d	Week 6±7d	D49*(inf+21)±3d	Week 8 (inf+28)±7d	Week 12 ±7d	M4 M5, ±14d	M6 M9 M12 ±14d	M18 ±14d	M24 M36 M48 ±14d	M60±14d	See footnote ¹	Post relapse ²	q3M		
Protocol defined AE and AESI, including new malignancies	D	16.2.													For patients that receive tisagenlecleucel, starting 8 weeks after tisagenlecleucel or prior to start of new anticancer therapy, whichever comes first							X	X		
Pregnancy Reporting	S	10.1.4.	Continuous																		X	X			
Laboratory assessments																									
Central Hematology	D	8.4.1.		X		X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X			
Central Chemistry	D	8.4.1.		X		X	X	X	X	X	X		X	X	X	X	X	X	X	X	X				
Central Cardiac Enzymes	D	8.4.1.		X				X					X	X	X	X	X	X	X	X					
Serum or Urine pregnancy test	S	8.4.1.	X serum	X serum	X serum						X		X	X			X (monthly testing between visits, M60/EOS visit must be serum testing)				X	X			
Central Coagulation (PT, aPTT, INR, fibrinogen, D-dimer)	D	8.4.1.				X			X		X			X	X	X					X				

Phase Crossover						Tisagenlecleucel Treatment and Follow up																		
Visit	Category	Protocol Section	Optional Bridging Chemo	Lymphodepleting Chemotherapy	Pre-tisagenlecleucel Infusion	Tisagenlecleucel Infusion	Post-tisagenlecleucel infusion (*See Section 8 for additional details regarding the timing of these visits)														End of Treatment and Primary Follow- up	Safety Follow-up ¹	Long term additional Follow-up ²	Survival Follow-up
Study day			D1-D21±7d	D22 to D25* (inf-6 to inf-3	D27* (inf-1)	D28*(inf)	D29*(inf + 1)	D31*(inf+3) ±1d	D34*(inf+6) ±1d	D38*(inf+10) ±3d	D41*(inf+13) ±3d	Week 6±7d	D49*(inf+21)±3d	Week 8 (inf+28)±7d	Week 12 ±7d	M4 M5, ±14d	M6 M9 M12 ±14d	M18 ±14d	M24 M36 M48 ±14d	M60±14d	See footnote ¹	Post relapse ²	q3M	
Central Serum immunoglobulin levels (IgG, IgA, IgM)	D	8.4.1.									X			X	X	X	X							
Rapid Influenza (A and B) Testing	D	8.4.1.		Within 10d to planned infusion																				
Urine Dipstick	D	8.4.1.	X	X			X																	
Tisagenlecleucel cellular kinetics, biomarker and safety assessments																								
Tisagenlecleucel cellular kinetics by qPCR (PB)	D	8.5.2.							X	X	X		X	X	X	X M4 only	X	X	X	X		X	X	
Tisagenlecleucel cellular kinetics by flow cytometry (Peripheral Blood)	D	8.5.2.							X	X	X		X	X	X	X M4 only	X	X	X	X			X	
Tisagenlecleucel cellular kinetics Bone Marrow (qPCR)	D	8.5.2.												X		X M4 only	As clinically indicated							

Phase Crossover						Tisagenlecleucel Treatment and Follow up																		
Visit	Category	Protocol Section	Optional Bridging Chemo	Lymphodepleting Chemotherapy	Pre-tisagenlecleucel Infusion	Tisagenlecleucel Infusion	Post-tisagenlecleucel infusion (*See Section 8 for additional details regarding the timing of these visits)														End of Treatment and Primary Follow-up	Safety Follow-up ¹	Long term additional Follow-up ²	Survival Follow-up
Study day			D1-D21±7d	D22 to D25* (inf-6 to inf-3)	D27* (inf-1)	D28*(inf)	D29*(inf + 1)	D31*(inf+3) ±1d	D34*(inf+6) ±1d	D38*(inf+10) ±3d	D41*(inf+13) ±3d	Week 6±7d	D49*(inf+21)±3d	Week 8 (inf+28)±7d	Week 12 ±7d	M4 M5, ±14d	M6 M9 M12 ±14d	M18 ±14d	M24 M36 M48 ±14d	M60±14d	See footnote ¹	Post relapse ²	q3M	
Tisagenlecleucel cellular kinetics - Bone marrow (flow cytometry)	D	8.5.2.												X		X M4 only	As clinically indicated							
Immunogenicity (serum)	D	8.5.2.			X						X			X		X M4 only	M6 and M12	X	M24 only	X				
Immunogenicity (Peripheral Blood)	D	8.5.2.			X						X			X		X M4 only	M6 and M12	X	M24 only	X		X		
RCL by VSV-g q- PCR	D	8.4.5.		X											X		X	X	X	X		X		
Tumor biopsy (CD19 expression, PD1, PDL1, IDO1, gene expression profiling)	D	8.5.3.											Mandatory per sampling schedule in Table 8-23 and at relapse and progression if accessible and does not impact treatment											
Immunophenotyping, Ig deep sequencing, gene expression-Peripheral Blood	D	8.5.3.		X	X				X	X				X	X		X	X	X	X			X	

Phase Crossover						Tisagenlecleucel Treatment and Follow up																	
Visit	Category	Protocol Section	Optional Bridging Chemo	Lymphodepleting Chemotherapy	Pre-tisagenlecleucel Infusion	Tisagenlecleucel Infusion	Post-tisagenlecleucel infusion (*See Section 8 for additional details regarding the timing of these visits)													End of Treatment and Primary Follow-up	Safety Follow-up ¹	Long term additional Follow-up ²	Survival Follow-up
Study day			D1-D21±7d	D22 to D25* (inf-6 to inf-3)	D27* (inf-1)	D28*(inf)	D29*(inf + 1)	D31*(inf+3) ±1d	D34*(inf+6) ±1d	D38*(inf+10) ±3d	D41*(inf+13) ±3d	Week 6±7d	D49*(inf+21)±3d	Week 8 (inf+28)±7d	Week 12 ±7d	M4 M5, ±14d	M6 M9 M12 ±14d	M18 ±14d	M24 M36 M48 ±14d	M60±14d	See footnote ¹	Post relapse ²	q3M
Peripheral blood (B and T cells levels-central assessment)	D	8.5.3.		X	X				X	X	X				X		M6 and M12	X	X	X		X	
Tisagenlecleucel cell product sample for correlative studies	D	8.5.3.		X																			
Electronic Patient Reported Outcomes (ePRO)																							
SF-36v2 (Acute Form)	D	8.5.1.1.	X									X		X	X		X	X	X	X ³		X ³	
EQ-5D-5L	D	8.5.1.3.	X									X		X	X		X	X	X	X ³		X ³	
FACT-Lym	D	8.5.1.2.	X									X		X	X		X	X	X	X ³		X ³	
Healthcare resource utilization	D	8.5.1.4.	Continuous until Month 6																				
Survival Follow-up	D	9.2.	For all patients who crossover, follow-up for survival every 3 months until the end of study (defined as the last visit for the last patient randomized). If a patient misses a quarterly scheduled visit where survival status is required, or if the time-point does not align with a scheduled visit, survival status can be obtained via phone contact																				
Disposition (End of Phase)	D	9.1.2.																		X		X	

Phase Crossover						Tisagenlecleucel Treatment and Follow up																		
Visit	Category	Protocol Section	Optional Bridging Chemo	Lymphodepleting Chemotherapy	Pre-tisagenlecleucel Infusion	Tisagenlecleucel Infusion	Post-tisagenlecleucel infusion (*See Section 8 for additional details regarding the timing of these visits)														End of Treatment and Primary Follow-up	Safety Follow-up ¹	Long term additional Follow-up ²	Survival Follow-up
Study day			D1-D21±7d	D22 to D25* (inf-6 to inf-3)	D27* (inf-1)	D28*(inf)	D29*(inf + 1)	D31*(inf+3) ±1d	D34*(inf+6) ±1d	D38*(inf+10) ±3d	D41*(inf+13) ±3d	Week 6±7d	D49*(inf+21)±3d	Week 8 (inf+28)±7d	Week 12 ±7d	M4 M5, ±14d	M6 M9 M12 ±14d	M18 ±14d	M24 M36 M48 ±14d	M60±14d	See footnote ¹	Post relapse ²	q3M	
<p>1 The safety follow-up visit should occur 8 weeks after last treatment administration or prior to starting new anticancer therapy, whichever occurs first. After this safety visit occurs, adverse events and concomitant medications will follow-up a modified reporting criteria in patients that receive tisagenlecleucel (Section 16.3 Appendix 3).</p> <p>2 Patients that receive tisagenlecleucel and have BIRC-confirmed PD/SD prior to Month 60 will be followed to collect key safety data every 3 months until M12, then every 6 months until M24, then yearly until M60. All visits may occur ±14 days.</p> <p>3 Patients that experience BIRC-confirmed PD/SD prior to Month 60 should complete PROs at the end of treatment visit, 4 weeks after PD/SD ±7 days , 12 weeks after PD/SD ±14 days, and 6 months after PD/SD ±14 days. If these timepoints align with scheduled long term additional follow-up visits they may be completed at the same time.</p>																								

8.1 Screening

Patient identification

Prior to signing ICF, when an investigator identifies a potential patient for CCTL019H2301, the site will contact the sponsor to inquire about tisagenlecleucel manufacturing slot availability within 3-6 weeks. If there is manufacturing slot availability and the patient is deemed a candidate to start second line treatment after randomization then the site should proceed to ICF signature within 48 hours of this contact.

Screening

Patients must sign the IRB/EC approved informed consent form (ICF) before any study specific screening procedures. Screening assessments to determine eligibility should be performed as per the visit evaluation schedule detailed in [Table 8-1](#). Randomization should occur when all clinical eligibility has been completed.

Patients who have signed an informed consent will be registered in the IRT system and undergo a routine lymphoma staging workup including all screening assessment outlined in [Table 8-1](#).

The assessments below do not need to be repeated if performed in the context of the leukapheresis procedure or if performed as part of clinical routine within 4 weeks of the patient signing the ICF:

- a. Central flow cytometry
- b. Serum immunoglobulin levels (IgG, IgA, IgM)
- c. Viral serology (EBV, HIV, HbsAg, HBsAb, HBcAb, HCVAb). If HIV screening test is positive then a confirmatory HIV test is required to be performed as per current local guidelines (see [Section 16.1](#) Appendix 1 for interpretation of hepatitis B and hepatitis C results). All viral serology must be repeated, if the interval between testing prior to lymphodepletion and tisagenlecleucel infusion exceeds 8 weeks or prior to switching a patient from SOC to tisagenlecleucel. **Note:** In general, the risk of hepatitis B reactivation is increased in patients with B cell depletion. Patients with latent or active hepatitis B are typically excluded from tisagenlecleucel treatment protocols. However, infection could potentially occur following the treatment trial completion or early withdrawal. Therefore, patients with a history of hepatitis B should be closely monitored for clinical and laboratory signs of active HBV infection (see [Section 16.1](#) Appendix 1).
- d. Disease assessments: Any imaging assessments, bone marrow biopsies, or lumbar punctures already completed during the regular work-up of the subject within 4 weeks prior to randomization, including before signing the main study ICF, can be considered as the screening disease assessments for this study. Any imaging or disease assessments obtained after randomization cannot be considered for screening. The patient should not receive any anticancer therapy between the screening disease assessments and randomization.

Rescreening is not allowed (patient who was screen failed cannot sign a new ICF) however laboratory parameters or other screening parameters may be retested within the screening period for an individual patient.

In the case where a safety laboratory assessment at screening outside of the range specified in the exclusion criteria, the assessment may be repeated once prior to randomization. If the repeat value remains outside of the specified ranges, the subject must be excluded from the study.

In the case of a logistical error (e.g. temperature control breach during apheresis shipping, contamination of cell culture, etc) which compromises the manufacture of a patient's tisagenlecleucel product, all screening procedures including collection of a new leukapheresis product can be repeated. In the event of a case that you feel qualifies as a logistical error, please consult with the Novartis medical monitor prior to repeating screening procedures for the patient.

Leukapheresis

Leukapheresis will be scheduled for cell procurement prior to final enrollment. It is strongly recommended to schedule leukapheresis prior to any planned chemotherapy or non-physiologic dose of steroids as an absolute T-cell count (absolute lymphocyte count multiplied by the percentage of CD3 positive lymphocytes) $\leq 300/\text{mm}^3$ may result in a poor T-cell collection and manufacturing failure.

The leukapheresis collection should be registered in IRT.

Cryopreserved non mobilized leukapheresis products collected prior to study entry (historical) may be used for tisagenlecleucel manufacturing if collected at a certified apheresis center and if the product is acceptable for manufacturing.

For patients who undergo leukapheresis collection on study after signing ICF, the following criteria must be met prior to leukapheresis collection:

1. Peripheral blood absolute lymphocyte count (ALC) $\geq 500/\mu\text{L}$ ($0.5 \times 10^9/\text{L}$), or if ALC $< 500/\mu\text{L}$ ($< 0.5 \times 10^9/\text{L}$), then the absolute CD3 lymphocyte count must be $\geq 150/\mu\text{L}$
2. No active or prior hepatitis B or C as indicated by serology within 1 week prior to leukapheresis collection (for detailed criteria see [Appendix 1](#))
3. The following treatments/medications should be stopped as follows:
 - Cytotoxic chemotherapy drugs must not be given within 2 weeks of leukapheresis
 - Intrathecal chemotherapy (IT) should be stopped ≥ 7 days prior to leukapheresis
 - Steroids must be stopped > 72 hours or 5 half lives, whichever is greater prior to leukapheresis. However, physiological replacement doses of steroids (≤ 40 mg/day hydrocortisone or equivalent) are allowed
 - Immunomodulatory drugs (e.g. interferons, TNF inhibitors): should be stopped ≥ 2 weeks prior to leukapheresis

Following informed consent, information on the patient's leukapheresis material including sample sentinel vials collected from leukapheresis (when available) will be sent to Novartis manufacturing separately or together with leukapheresis product. Final enrollment is defined

as the point at which the patient meets all inclusion/exclusion criteria, and the patient is randomized to a treatment arm.

Please refer to the Leukapheresis Key Requirements within the most recent [\[Investigational Leukapheresis, Cryopreservation and Scheduling Manual\]](#) for more detailed instructions on optimal timing of leukapheresis collection and the recommended procurement, handling and shipment procedures of the leukapheresis samples to the designated manufacturing facility. Drugs prohibited prior to leukapheresis and tisagenlecleucel infusion are described in [Section 6.2.2](#).

8.1.1 Eligibility screening

Only following informed consent to study CCTL019H2301 and confirmation of all eligibility criteria will information on the patient's leukapheresis product be transferred to the Novartis designated manufacturing facility.

For sites performing the leukapheresis as part of this protocol leukapheresis can only be performed after patient consent has been obtained. At the time when manufacturing of tisagenlecleucel is required (by randomization or crossover), a Novartis designated manufacturing facility will then evaluate the patient's leukapheresis product for acceptance. The acceptance of the product will be registered in IRT by Novartis personnel.

Randomization will occur at the point at which a patient meets all inclusion/exclusion criteria and registers the call in IRT. The patient is then randomized using the same Subject Number assigned at screening by the site investigator or designated staff. Once assigned, the Subject Number must not be reused for any other patient and the Subject Number for that individual must not be changed. If a screened patient is not randomized for any reason, the specific reason will be entered into the clinical database on a disposition CRF.

At randomization, patients will be stratified by response to first line treatment (refractory or relapsed within 6 months from last dose of first line immunochemotherapy, and relapsed 6 to 12 months from last dose of first line immunochemotherapy) and by IPI (<2 v ≥ 2) per local investigator assessment and randomized in IRT.

For detailed screening, and randomization procedures, related to the use of Interactive Response Technology (IRT), please refer to the [\[IRT User Manual\]](#).

8.1.2 Information to be collected on screening failures

Subjects who sign an informed consent form and subsequently found to be ineligible prior to randomization will be considered a screen failure. The reason for screen failure should be recorded on the appropriate Case Report Form. The demographic information, informed consent, leukapheresis collection information, and Inclusion/Exclusion pages must also be completed for screen failure subjects. No other data will be entered into the clinical database for subjects who are screen failures, unless the subject experienced a serious adverse event (see SAE section for reporting details) or an adverse event which leads to discontinuation during the screening phase. If the subject fails to be randomized, the IRT must be notified within 2 days of the screen fail that the subject was not randomized.

Subjects who are randomized and fail to start treatment, e.g. subjects randomized in error, will be considered an early terminator. The reason for early termination should be recorded on the appropriate Case Report Form.

8.2 Subject demographics/other baseline characteristics

Country specific regulations should be considered for the collection of demographic and baseline characteristics in alignment with CRF.

Subject demographic and baseline characteristic data are to be collected on all subjects. Relevant medical history/current medical condition present before signing the informed consent will be recorded. Investigators will have the discretion to record abnormal test findings on the appropriate CRF whenever in their judgment, the test abnormality occurred prior to the informed consent signature.

8.3 Efficacy

Efficacy assessments will be performed as indicated in [Table 8-1](#), [Table 8-2](#), and [Table 8-3](#), and as clinically indicated until crossover, relapse, progression, death, lost to follow up or withdrawal of consent. After crossover, efficacy will continue to be assessed by local investigator as per [Table 8-4](#). Efficacy evaluation will be collected as described in [Table 8-5](#) based on recommendations by the International Malignant Lymphomas Imaging Working Group ([Cheson et al 2014](#); [Barrington et al 2014](#)) and detailed in [Section 16.2](#) Appendix 2.

A Blinded Independent Review Committee (BIRC) appointed by Novartis will review data related to disease response assessment according to the Novartis Guideline for Efficacy Evaluation in lymphoma studies, version 2. The BIRC will review all data related to disease response for all randomized patients. Sites should request expedited review of imaging files under the conditions described in [Section 8.3.3](#). Patients who crossover to Arm A will not be assessed by BIRC. Radiological imaging will be transmitted by the sites to the imaging Contract Research Organization (CRO) designated by Novartis to undergo quality checks and central review by the BIRC. Clinical data such as, physical exam, bone marrow results, pathology/histology and cytology results; as well as, information regarding prior interventions, pre-existing radiographic findings that may mimic metastatic disease at baseline/screening and on-study interventions will be transmitted to the imaging CRO for review by a medical oncologist/hematologist. At BIRC, during the overall review the available clinical data will be integrated with the pathological and radiological response data to provide the overall disease response:

The presence of one (1) or more stable, but persistent clinical lesions will downgrade a radiology CR to an overall PR.

The presence of one (1) or more new or worsening clinical lesions will result in Overall PD.

If bone marrow biopsy is not negative, a radiographic timepoint response (TPR) of CR at that time point would be downgraded to an overall PR.

A new lesion biopsy result indicating a malignancy would result in overall PD, if not already assessed as PD during the radiology review.

For any given time point, any clinical listings that are within a +14 day window (+28 day window for bone marrow data) of the radiographic time point date can be used for the corresponding oncology time point assessments. Clinical listings that are +15 days after a radiographic time point will be grouped with the next radiographic time point. For example, if the radiographic time point date is 01-Mar, and the non-bone marrow clinical evaluations on the listings occur on 10-Mar and 16-Mar, the listings from 10-Mar will be associated with the radiographic time point date of 01-Mar. The listings from 16-Mar will not be associated with the 01-Mar radiographic time point and will be grouped with the next radiographic time point. Any clinical listings that fall outside the allowable window will be evaluated with the next radiographic time point.

For bone marrow data, the assessment window will be extended to +42 days if there are no subsequent radiographic time points. This +42 day window will only apply to overall assessments associated with the subject's last radiographic time point.

Further details regarding the BIRC assessment will be provided in the BIRC charter.

The central review of the scans will be carried out in a blinded fashion. The decision regarding patient management will remain with the local investigator. Enrollment eligibility will be determined by the local staging assessment of the required images obtained during screening. Imaging studies used to determine eligibility must be submitted to the BIRC.

Disease characterization at baseline and evaluation of efficacy during study rely on the following:

1. Pathology assessment
2. Imaging
3. Bone marrow biopsy or aspirate
4. CSF cytology
5. Lesions from physical exam findings
6. Procedures performed on study

Imaging data will be centrally collected and checked for quality by an imaging Contract Research Organization (CRO) designated by Novartis. The results of the central evaluations will be used for primary analysis purposes. The local investigator's assessment will be used for treatment decision making.

Any potentially measurable lesion that has been previously treated with radiotherapy should be considered as a non-measurable (non-index) lesion. However, if a lesion previously treated with radiotherapy has clearly progressed since the radiotherapy, it can be considered as a measurable lesion.

Imaging assessments

Imaging assessments will be performed at screening within D-14 to -1 of randomization. Screening/baseline imaging assessment should be done as close to randomization as possible. In the event more than one imaging assessment is performed after ICF and prior to randomization then only the assessment date closest to randomization should be captured in the clinical database and used as the screening/baseline assessment.

Any imaging assessments, bone marrow biopsies, or lumbar punctures already completed during the regular work-up of the subject within 4 weeks prior to randomization, including before signing the main study ICF, can be considered as the screening disease assessments for this study. Any imaging or disease assessments obtained after randomization cannot be considered for screening. The patient should not receive any anticancer therapy between the screening disease assessments and randomization. One of the following assessments are required at screening, Week 12, and Month 6 and at other timepoints only for new CR on CT scan not previously documented to confirm response:

1. PET-CT with diagnostic CT
2. PET-CT with non-diagnostic CT + dedicated diagnostic CT
3. Dedicated diagnostic CT + dedicated FDG PET

PET imaging is always required in order to confirm the first documented complete response (CR). If the first documented radiological CR is seen on CT scan only, a confirmatory PET scan (either FDG PET or PET-CT) should be obtained within 14 days in order to confirm that timepoint's response of CR. If the PET scan is not obtained within 14 days, the timepoint must be assessed as a PR, and the next scan should be done by one of the 3 methods above as soon as possible to confirm the CR. Once CR has been established by PET imaging, subsequent CR and/or PD may be followed by CT imaging only.

The CT component of the PET-CT may be used in lieu of a standalone CT/MRI, only if the CT component is of similar diagnostic quality as a contrast enhanced CT performed without PET. If contrast enhanced PET-CT with diagnostic CT is not available, a standard FDG-PET must be performed and a standalone diagnostic CT/MRI should be performed in addition to the FDG-PET scan. If independent CT and PET scanners are used, and the subject is receiving both scans on the same day, the PET must be performed prior to the CT with IV contrast as to not compromise PET results. The PET-CT acquisition methodology (e.g., administration of intravenous contrast) should remain consistent at all imaging visits for any given patient.

It is preferred to obtain a PET-CT with diagnostic CT at all protocol required imaging visits when possible.

If a subject is known to have a contraindication to CT intravenous (IV) contrast media or develops a contraindication during the trial, a non-contrast CT of the neck and chest (MRI is not recommended due to respiratory artifacts, however if CT is not feasible per local regulations, MRI can be performed instead) plus a contrast-enhanced MRI (if possible) of the abdomen and pelvis should be performed.

Brain MRI or CT should be completed if clinically indicated at screening and post infusion. Contrast enhanced brain MRI is preferred, however, if MRI contrast is contraindicated, then MRI without contrast or CT with/without contrast is acceptable.

If skin lesions are present as a result of a physical exam, these are to be documented via the Lugano classification 2014 assessment as a physical exam, skin lesion.

Additional imaging assessments may be performed at any time during the study at the investigator's discretion for suspicion of PD or to support the efficacy evaluations for a subject, as necessary. If imaging is done for safety reasons only there should be no efficacy

assessment and/or submission to the imaging CRO. (All imaging submitted to the imaging CRO are expected to have a corresponding local efficacy assessment).

Any on protocol scheduled and/or unscheduled imaging assessments done within \pm 14 day window are to be assessed under a single evaluation.

Clinical suspicion of disease progression at any time requires a physical examination and imaging assessments to be performed promptly rather than waiting for the next scheduled imaging assessment.

Table 8-5 Imaging or disease assessment collection plan

Procedure	Screening	Treatment Assessment
PET-CT with contrast enhanced diagnostic (Dx) CT - Neck, Chest, Abdomen, Pelvis	Mandated	Mandated at Week 12, and at Month 6 May be used within 14 days at any visit a new CR by CT needs to be confirmed, not seen previously Once CR is confirmed with PET, additional PET imaging is not required (CT only)
Dedicated FDG PET	Mandated, if no PET-CT available	Mandated at Week 12, and Month 6, if no PET-CT is available May be used within 14 days at any visit a new CR by CT needs to be confirmed, not seen previously Once CR is confirmed with PET, additional PET imaging is not required (CT only)
CT/MRI (Neck, Chest, Abdomen, Pelvis)	Mandated, if no Dx PET-CT available	Mandated at Week 6, months 9, 12, 18, 24, 36, 48 and 60/EOT and any time to confirm PD or response. PET-CT with diagnostic CT is preferred at all imaging visits when possible.
Response (CR) confirmation by PET-CT or dedicated FDG PET	NA	PET imaging is required \pm 14 days within the same CT timepoint window when CR is seen by CT, only for new CR and not previously documented. Once CR has been confirmed PET imaging is no longer needed, however it is the preferred method when possible.
CT/MRI brain	As clinically indicated	As clinically indicated
Bone marrow aspirate and/or biopsy cells	Mandated	Mandated to confirm CR if bone marrow was involved by lymphoma prior infusion and as clinically indicated
Tumor biopsy (FFPE) for pathology assessment and subtype determination	Mandated	n/a
Tumor biopsy (for exploratory assessments)	Mandated	Recommended if PET shows residual metabolically active tissue to rule out interference of tisagenlecleucel activity with PET results.
CSF Cytology	Mandated	As clinically indicated

The status of primary malignancy based on clinical routine assessments will be recorded for patients with ongoing response during follow up. The CD19 status at time of relapse should be recorded.

8.3.1 Transmission of efficacy data to BIRC

All radiological assessments will be read locally and should be submitted promptly after acquisition to the imaging vendor designated by Novartis. Rapid image transmission to the

central imaging vendor will be accomplished by transferring the images acquired by the investigator electronically in a secured website (e.g.: via the internet). In all instances, the process at the imaging vendor will ensure that the central reviewers remain blinded to the treatment arm, the results of the local assessment, and the expedited nature of the review.

8.3.2 Non-expedited review - timepoints without locally determined progression or stable disease

All imaging time points without locally determined progression or stable disease per Lugano classification 2014 will be read on an ongoing non-expedited basis as detailed in the imaging manual to be provided by the designated imaging vendor and independent review charter. Expedited review may be required if necessary. Results of these readings will not be communicated to the sites.

8.3.3 Expedited review - timepoints with locally determined progression or stable disease

All patients who have disease progression determined by the local investigator at any time per Lugano classification 2014 require an expedited central tumor response review by the BIRC. All patients who have stable or progressive disease per Lugano classification 2014 determined by the local investigator require an expedited central tumor response review by the BIRC. In these cases described above, the investigator must seek an expedited review and indicate this request to the imaging vendor on a designated form or by alternative means identified by the imaging vendor. The imaging CRO will ensure that the BIRC reviewers are blinded to the results of the local assessments and the nature of the expedited review.

Rapid image transmission to the imaging CRO may be accomplished by uploading all digital images acquired by the Investigator to the secure website provided by the imaging CRO (e.g., via the internet). The imaging will undergo expedited central review (within 5 business days from the time of the receipt of images at the imaging CRO and once all applicable image queries are resolved) and the results of the central review will be communicated to the site. While the investigator is awaiting the results of the BIRC from the imaging CRO confirming disease progression or stable disease, it is preferable that the patient continue on study treatment. However, during this time, the investigator should do whatever is medically necessary for his/her patient.

In patients randomized to Arm B:

- If the central review confirms disease progression or stable disease at or after the week 6 (± 1 w) assessment, then the physician may request a tisagenlecleucel manufacturing slot from the SPONSOR and change therapy as appropriate.
- If the central review confirms disease progression or stable disease at or after the week 12 (± 1 w) assessment, then the patient may cross over from SOC treatment to tisagenlecleucel treatment strategy.

Treatment may be continued beyond Lugano classification 2014 defined PD determined by the investigator and confirmed by the BIRC, if, in the judgment of the investigator, there is evidence of clinical benefit and the patient wishes to continue on the study treatment and meets the pre-infusion criteria outlined in [Section 6.1.2](#).

If the central review does not determine disease progression or stable disease per Lugano classification 2014, the patient should continue to have imaging performed as per protocol and receiving the study treatment until the central review determines progressive disease or stable disease unless there is a medical need (i.e., clinical deterioration) for an immediate change in therapy per the investigator's clinical judgment.

8.4 Safety

Physical assessments are specified below in [Table 8-6](#), with the assessment schedule detailing when each assessment is to be performed.

For details on AE collection and reporting, refer to [Section 10.1](#).

Table 8-6 Physical assessments

Assessment	Specification
Physical examination	A complete evaluation will generally include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities and vascular and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed. Significant findings that were present prior to the signing of informed consent must be included in the appropriate CRF page. Any lesions, detected during a physical exam at any time-point that are not detectable by imaging should be recorded on the appropriate CRF page as a non-targeted lesion and does not need to be recorded on the appropriate CRF page. Significant new findings, other than new lesions, that begins or worsens after informed consent must be recorded on the appropriate CRF page.
Vital sign	Vital signs include temperature, blood pressure, pulse rate, respiratory rate, and pulse oximetry. For patients receiving tisagenlecleucel, vital signs (temperature, respiration rate, pulse rate, pulse oximetry, and blood pressure) will be taken prior to, during and immediately after the infusion and then approximately every 15 minutes for one hour and then every hour for the next two hours, or until these signs are satisfactory and stable. Fever is frequently the first symptom of CRS and must be monitored following infusion. For all patients, systolic and diastolic blood pressure should be measured after the patient has been sitting for five minutes, with back supported and both feet placed on the floor, using an automated validated device, with an appropriately sized cuff. In case the cuff sizes available are not large or small enough for the patient's arm circumference, a sphygmomanometer with an appropriately sized cuff should be used.
Height and weight	Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram [kg] in indoor clothing, but without shoes) will be measured.

ECOG Performance status grade will be used as described in the [Table 8-7](#).

Table 8-7 ECOG performance status grade

Grade	ECOG
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

8.4.1 Laboratory evaluations

Laboratory assessments are specified below in [Table 8-8](#), with the assessment schedule detailing when each assessment is to be performed.

Weekly sample collections for serum cytokines, tisagenlecleucel cellular kinetics, and inflammatory markers (e.g. ferritin and CRP) are mandated during the first 28 days following tisagenlecleucel infusion. However, as the time-course and rapidity of CRS development varies among patients, additional unscheduled samples for these markers may also be collected as needed, if it is clinically feasible. Frequent monitoring of serum CRP, ferritin and cytokines should be considered during the clinical course of CRS of any severity (e.g. every day to several days) especially around the following clinical events: initial persistence of fevers, hemodynamic instability, initial and worsening of respiratory distress, rapid clinical deterioration, just prior to and daily for 2 days following tocilizumab administration, around other clinically significant events and upon the clinical resolution of CRS.

Please note that results of cytokine analyses are NOT to be used for clinical management decisions of CRS. A detailed treatment algorithm has been established with clear criteria for CRS management (see [Table 6-2](#) and [Table 6-3](#)).

Table 8-8 Laboratory assessments

Test Category	Test Name
Hematology	Hematocrit, Hemoglobin, MCHC, MCV, Platelets, Red blood cells, White blood cells with complete differential (Basophils, Eosinophils, Lymphocytes, Atypical Lymphocytes, Monocytes, Neutrophils, Bands, Lymphoblasts, Plasma cells, Prolymphocytes, Myelocytes, Metamyelocytes, and Promyelocytes)
Chemistry	Glucose (fasting), Blood Urea Nitrogen (BUN), Creatinine, eGFR, Sodium, Potassium, Calcium, Magnesium, Phosphorous, Total Cholesterol, Triglycerides, Total Protein, Albumin, Total Bilirubin, Direct Bilirubin, Indirect Bilirubin, Amylase, Alkaline phosphatase, ALT (SGPT), AST (SGOT), Lipase, LDH, Ferritin, CRP, and Uric Acid
Cardiac Enzymes	Troponin I, NT-proBNP
Urinalysis	Macroscopic Panel (Dipstick) (Bilirubin, Blood, Glucose, Ketones, Leukocytes esterase, Nitrite, pH, Protein, Specific Gravity) If macroscopic panel is abnormal then perform microscopic panel (Red Blood Cells, White Blood Cells, Casts, Crystals, Bacteria, Epithelial cells)
Coagulation	Prothrombin time (PT) or International normalized ratio (INR), activated Partial thromboplastin time (aPTT), fibrinogen, and D-dimer
Influenza	Rapid Influenza A & B Test
Viral Serology	Epstein-Barr Virus (EBV), Hepatitis C Virus (HCV) antibody, Hepatitis B surface antigen (HBsAg), Hepatitis B surface antibody (HBsAb), Hepatitis B core antibody (HBcAb), HIV test (if an initial HIV screening test is positive then a confirmatory HIV test is required to be performed as per current local guidelines) Viral serology testing must be within 8 weeks prior to lymphodepletion and tisagenlecleucel infusion.
Additional tests	Serum immunoglobulin levels (IgG, IgA, IgM) Peripheral blood B cell and T cell levels will be done by flow cytometry. Flow cytometry on peripheral blood and leukapheresis product.
Pregnancy Test	Serum or urine tests
CD19	Immunohistochemistry or flow cytometry (Screening to randomization and as clinically indicated)
DLBCL and subtype determination	Immunohistochemistry (Screening to randomization)
c-myc, bcl-2 and bcl-6 expression	FISH (Screening to randomization) [as applicable]
Rituximab concentrations	Concentrations of rituximab (serum) – Patients receiving tisagenlecleucel (Arm A and crossover)

8.4.2 Electrocardiogram (ECG)

ECGs must be recorded after 10 minutes rest in the supine position to ensure stable baseline. The preferred sequence of cardiovascular data collection during study visits is ECG collection first, followed by vital signs, and blood draws. The Fredericia QT correction formula (QTcF) should be used for clinical decisions.

Single 12-lead ECGs are to be collected. The original ECGs on a non-heat-sensitive paper or a certified copy on non-heat sensitive paper, appropriately signed, must be collected and archived at the study site.

For any ECGs with subject safety concerns, two additional ECGs must be performed to confirm the safety finding. A monitoring or review process should be in place for clinically significant ECG findings throughout the study and especially at baseline before administration of study treatment.

Any identifier details must be redacted, e.g. subject initials, date of birth.

In the event that a clinically significant ECG abnormality is identified at the site (e.g. severe arrhythmia, conduction abnormality of QTcF ≥ 450 ms for males and QTcF ≥ 460 ms for females), the ECG is to be repeated to confirm the diagnosis. If the subject is hemodynamically compromised, the investigator or a medically qualified person must initiate appropriate safety procedures without delay (for example cardioversion).

Clinically significant abnormalities must be recorded on the CRF as either medical history/current medical conditions or adverse events as appropriate

A standard 12-lead ECG will be performed

- at screening prior to randomization
- prior to tisagenlecleucel infusion for patients randomized to Arm A or crossover patients
- as clinically indicated for patients randomized to Arm B

Interpretation of the tracing must be made by a qualified physician and documented on the appropriate CRF. Each ECG tracing should be labeled with the study number, subject initials (where regulations permit), subject number, date, and kept in the source documents at the study site. Clinically significant abnormalities present at screening should be reported on the appropriate CRF. Clinically significant findings must be discussed with Novartis prior to enrolling the subject in the study. New or worsened clinically significant findings occurring after informed consent must be recorded as adverse events.

Additional, unscheduled, safety ECGs may be repeated at the discretion of the investigator at any time during the study as clinically indicated. Unscheduled ECGs with clinically significant findings should be collected in triplicate. Local cardiologist ECG assessment may also be performed at any time during the study at the discretion of the investigator.

Clinically significant ECG abnormalities present at screening should be reported on the appropriate CRF. New or worsened clinically significant findings occurring after informed consent must be recorded as adverse events.

8.4.2.1 Cardiac imaging - MRA (magnetic resonance angiography)

An ECHO/MRA test is required to be completed at screening. Clinically significant abnormalities present when the patient signed the informed consent should be reported on the appropriate eCRF page. Clinically significant findings must be discussed with Novartis prior to enrolling the patient in the study. New or worsened clinically significant findings occurring after informed consent must be recorded on the Adverse Events CRF page. Patients must have a left ventricular ejection fraction (LVEF) $\geq 45\%$ to be included into the study.

8.4.2.2 Cardiac enzymes

Cardiac enzymes will be monitored throughout the study as per the appropriate visit evaluation schedule.

8.4.3 Pregnancy

A condom is required for all sexually active male participants to prevent them from fathering a child AND to prevent delivery of study treatment via seminal fluid to their partner. In addition, male participants should not donate sperm for the time period specified above.

All pre-menopausal women who are not surgically sterile will have pregnancy testing. Additional pregnancy testing might be performed if requested by local requirements. For the frequency of pregnancy testing please refer to [Table 8-2](#), [Table 8-3](#), and [Table 8-4](#). For all pregnancy tests performed at home, the site personnel will Follow-up with the subject via telephone call to collect the date and the test results and document the information in the subject's source documents.

To ensure subject safety, each pregnancy occurring once the subject has been infused with tisagenlecleucel must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy follow up in this study will end after birth or after any adverse pregnancy outcome associated with the end of the pregnancy. In case of live birth the newborn will be followed up until 12 months of age to detect any developmental issue or abnormality that would not be seen at birth. Pregnancy outcomes must also be collected for the female partners of any males who received tisagenlecleucel in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the oncology Novartis Chief Medical Office and Patient Safety (CMO&PS). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to tisagenlecleucel any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

Pregnancy outcomes should be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

For more information about the effects of tisagenlecleucel on reproduction please refer to the recent [Tisagenlecleucel Investigator's Brochure].

Assessments of fertility

Not applicable

8.4.4 Spirometry

In order to assess, ASCT eligibility, a FEV1 or DLCO test should be performed at screening according to local institutional practice.

8.4.5 Other safety evaluations

Humoral immunogenicity to tisagenlecleucel and detectable RCL will be assessed as described [Table 8-2](#) and [Table 8-4](#).

8.4.6 Appropriateness of safety measurements

The safety assessments selected are standard for this indication/subject population.

8.5 Additional assessments

8.5.1 Patient reported outcomes (PRO)

Three questionnaires will be used in this study to capture electronic patient reported outcomes (ePROs): the Short Form (36) Health Survey (SF-36 v2), the Functional Assessment of Cancer Therapy—Lymphoma (FACT-Lym version 4), and the EuroQol 5D (EQ-5D-5L) questionnaire.

Patient reported outcome data will be assessed during the study as indicated in [Table 8-1](#), [Table 8-2](#), [Table 8-3](#), and [Table 8-4](#). Descriptive statistics (e.g. mean, median and frequency) and change from baseline of the summary scores for each post baseline time-point/window of assessment will be provided by treatment arm. FAS will be used for all analysis.

Each of the questionnaires mentioned below is designed for patient self-administration. Method of activating and operating the data capture device is provided in a separate user guide.

The patient should be given the tablet to complete the questionnaire(s) at the scheduled visit prior to any testing, treatment, or discussion with the physician or clinical personnel. The patients refused to complete all or any part of a PRO measure should be documented in the study data capture systems and should not be captured as a protocol deviation. The questions should be completed in the language the respondent is most familiar with, at the scheduled visit before the patient sees the investigator for clinical assessments. The patient should be given sufficient space and time to complete the PRO measures.

The responsible site personnel should check the patients' responses for completeness and encourage the patient to complete any missing responses. The printed copy of the questionnaire will be kept with the patient's file as the source document. Detailed instructions relating to the administrative procedures of the questionnaires will be provided to the sites. Patient's refusal to complete all or any part of a questionnaire should be documented in the study data capture system.

The completed ePRO data and any unsolicited comments made by the patient should be reviewed and assessed by the investigator for responses which may indicate potential AEs, including SAEs, before any clinical study examinations. This assessment should be documented in study source records. If AEs or SAEs are confirmed, study investigators should not encourage the patient to change responses reported in the completed ePRO data.

Patients that crossover to the tisagenlecleucel arm will still need to complete the SF-36v2, FACT-Lym, and EQ-5D-5L at the same time points specified above and in [Table 8-4](#). The SF-36v2, FACT-Lym, and EQ-5D-5L should be collected at the EOT visit in patients that experience BIRC-confirmed PD/SD in Arm A (or patients that crossover from Arm B to Arm A), and in patients that experience BIRC-confirmed PD/SD in Arm B, but do not plan to crossover. Whenever possible, this collection should occur prior to initiation of new

anticancer therapy. These patients should also complete the SF-36v2, FACT-Lym, and EQ-5D-5L at 4 weeks after PD/SD, 12 weeks after PD/SD, and 6 months after PD/SD.

Study investigators must follow reporting instructions outlined in [Section 10.1](#).

8.5.1.1 SF-36 v2 (acute form)

The 36-item short form (SF-36v2) is a generic quality of life measure used widely in clinical practice and research, general population surveys and health policy evaluations ([Ware and Sherbourne 1992](#)). The SF-36 v2 comprises 36 questions, which are summarized in eight health domain scores: Physical Functioning, Role-Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role-Emotional, and Mental Health. Two overall component summary scores, the Physical Component Summary (PCS) and the Mental Component Summary (MCS), also can be computed. Domain and component summary scores can be converted to norm-based scores. A higher SF-36 score denotes better HRQoL.

The SF-36 has proven useful in monitoring general and specific populations, comparing the relative burden of different disease, differentiating the health benefits produced by different treatments, and in screening individual patients. Although a generic HRQoL measure, the SF-36 is sensitive to variations in specific health states (known groups validity). For example, a study documenting the long term effects of NHL and its treatment found that those with comorbid health conditions had lower SF-36 physical functioning scores than those without such conditions ([Mols et al. 2007](#)).

8.5.1.2 FACT-Lym version 4

The Functional Assessment of Cancer Therapy-Lymphoma (FACT-Lym) is a questionnaire to assess the quality of life in patients with Lymphoma. The FACT-Lym questionnaire is composed of the FACT-General (FACT-G) – a 27-item compilation of general questions scored on a 5 point scale ranging from 0 = “not at all” to 4 = “very much” - and an additional 15 items that assess patient concerns relating to lymphoma: FACT-Lym lymphoma-specific subscale (FACT-LymS; range, 0-60).

FACT-G items are divided into four primary HRQoL domains: PWB (Physical Well-Being; seven items, range 0-28), SWB (Social/Family Well-Being; seven items, range 0-28), EWB (Emotional Well-Being, six items, range 0-24), and FWB (Functional Well-Being and Additional Concerns; seven items range, 0-28).

The FACT-LymS consists of common lymphoma disease and/or treatment-related symptoms (e.g., pain, fever, swelling, night sweats, insomnia, itching, weight loss, fatigue, and loss of appetite). Two summary scales: FACT-Lym trial outcomes index (FACT-Lym TOI; range: 0-116; composed of the PWB, FWB, and FACT-Lym LYMS scales); FACT-Lym total score (FACT-Lym TS, range, 0-168; composed of all of the scales) can also be calculated. Negatively worded items are reverse scored prior to summing so that higher scores are reflective of better HRQoL.

This scale is designed for patient self-administration. Patients should be instructed to read the brief. After the patient's correct understanding has been confirmed they should be encouraged to complete every item in order without skipping any. Some patients may feel that a given

question is not applicable to them and therefore will skip the item altogether. Patients should be encouraged to check the response most applicable.

8.5.1.3 EQ-5D-5L

The EQ-5D-5L is a widely used, self-administered questionnaire designed to assess health status in adults. The measure is divided into two distinct sections. The first section includes one item addressing each of five dimensions (mobility, self-care, usual activity, pain/discomfort, and anxiety/depression). Patients report each of these items from “no problem”, “slight problem”, “moderate problem”, “severe problem”, or “extreme problem.” A composite health index is then defined by combining the levels for each dimension. The second section of the questionnaire (EQ-VAS) measures self-rated (global) health status utilizing a vertically oriented visual analogue scale where 100 represents the “best possible health state” and 0 represents the “worst possible health state.” Respondents are asked to rate their current health by placing a mark along this continuum. The recall period is “today,” and the questionnaire requires 5 to 10 minutes to complete.

8.5.1.4 Healthcare resource utilization regarding hospitalization

Hospitalizations will be evaluated in this study as an exploratory endpoint to characterize the impact of study treatment on this aspect of healthcare resource utilization. These data may be used to support assessments used to characterize the economic impact of study treatment regimens.

Hospitalization data of interest will focus on those hospitalizations reported within the first 6 months after treatment. Hospitalizations as a result of the following reasons are not to be reported:

- Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
- Social reasons and respite care in the absence of any deterioration in the patient’s general condition
- Treatments occurring on an emergency outpatient basis that does not result in hospital admission and involves an event not fulfilling any of the definitions of a SAE as described in [Section 10.1.2](#).

Healthcare resource utilization data regarding hospitalizations should be captured from randomization (Day 1) up to Month 6 for the patient as described in [Table 8-1](#), [Table 8-2](#), [Table 8-3](#), and [Table 8-4](#).

Information related to the length of stay (e.g., dates of admission or discharge), hospital ward facilities used (e.g., emergency department, intensive care unit, general ward, etc.), reasons for hospitalization as associated with the study treatment regimen, disease and/or disease progression, or any other reason will be of interest; and hospital discharge information will be evaluated.

8.5.2 Pharmacokinetics

PK samples will be collected in all subjects at the visits defined in the assessment schedule. Follow instructions outlined in the laboratory manual regarding sample collection, numbering, processing and shipment. See the potential use of residual samples for more information.

In order to better define the PK profile, the timing of the PK sample collection may be altered based on emergent data.

The number of samples/blood draws and total blood volume collected will not exceed those stated in the protocol.

Tisagenlecleucel transgene and surface expression measurement

Tisagenlecleucel concentrations in peripheral blood (and bone marrow and CSF if available) will be listed, graphed and summarized by time points as assessed by the following:

- Tisagenlecleucel transgene levels as measured by q-PCR
- Tisagenlecleucel transduced cells measured by flow cytometry of CD3-positive/ CD4-positive and CD3-positive/CD8-positive tisagenlecleucel transduced cells if feasible.

The cellular kinetics parameters listed in [Table 8-9](#) along with other relevant cellular kinetics parameters will be estimated, if feasible, from the individual concentration versus time profiles using a non-compartmental approach within the modeling program Phoenix WinNonlin® Version 6.4 (Pharsight, Mountain View, CA) and reported by response category. The non-quantifiable concentrations will be imputed to zero for PK concentration summaries, and will not be included for estimation of cellular kinetics parameters. Results reported but deemed unreliable will be flagged and excluded from the summaries and cellular kinetics parameter derivations.

Descriptive statistics of cellular kinetics parameters (arithmetic and geometric means, standard deviation, CV%, CV% geometric mean, minimum, median and maximum) will be summarized by best overall response for Arm A. For T_{max} only minimum, median and maximum will be presented.

The linear trapezoidal linear interpolation rule will be used for AUC calculation. Regression analysis of the terminal plasma elimination phase for the determination of $T_{1/2}$ will include at least 3 data points after C_{max} . If the adjusted R^2 value of the regression analysis of the terminal phase will be less than 0.6, no values will be reported for $T_{1/2}$.

Table 8-9 Non compartmental cellular kinetics parameters

Parameter	Definition
AUC 0 - 28d and/or AUC0-84d	The AUC from time zero to day 28 and/or day 84 and or other disease assessment days, in peripheral blood (%*days or days*copies/ µg)
C _{max}	The maximum (peak) observed in peripheral blood or other body fluid drug concentration after single dose administration (% or copies/ µg)
T _{max}	The time to reach maximum (peak) peripheral blood or other body fluid drug concentration after single dose administration (days)
T _{1/2}	The half-life associated with the elimination phase slope of a semi logarithmic concentration-time curve (days) in peripheral blood
C _{last}	The last observed quantifiable concentration in peripheral blood (% or copies/ug)
T _{last}	The time of last observed quantifiable concentration in peripheral blood (days)

Summary of cellular kinetics by CRS grade and use of tocilizumab

For patients who receive tocilizumab for management of CRS, the cellular kinetic parameters will be summarized by use of tocilizumab and CRS grades.

Rituximab

The rituximab concentrations will be summarized by response for each time point.

Concentrations below the lower limit of quantification (LLOQ) will be reported as “zero” and missing data will be labeled as such in the Bioanalytical Data Report.

PK samples will be collected at the visits defined in the assessment schedule. Follow instructions outlined in the central laboratory manual regarding sample collection, numbering, processing and shipment. See the potential use of residual samples for more information.

The number of samples/blood draws and total blood volume collected will not exceed those stated in the protocol.

Table 8-10 Validated analytical methods and limit of quantification associated with the PK analytes and immunogenicity assessments

Analyte	Analytical method	Units	Lower limit of quantification (LLOQ)	Type of biological sample	Dataset	Vendor
tisagenlecleucel transgene	Quantitative polymerase chain reaction (qPCR)	copies/ug	10 copies/reaction equivalent to approx. 50 copies/ug of genomic DNA	Peripheral blood	PAS	Navigate
Surface expression of CAR positive cells	Flow cytometry	% of CD3+ T cells	0.5% of CD3+ T cells	Peripheral blood	PAS	Navigate
Rituximab	ELISA	ng/mL	313 ng/mL	Serum	RPAS	Wuxi
Anti-mCAR antibodies (Humoral immunogenicity)	Flow cytometry	MFI (mean fluorescence intensity)	NA Response compared to respective CP defined during validation	Serum	Safety set	PRA
Antigen specific T cell lymphocytes (Cellular immunogenicity)	Intracellular Interferon gamma staining and flow cytometry	% IFNgamma+ CD4/CD8 T cells (for both pool 1 and pool 2)	IFNgamma+ CD4 T cells: LLOQ for SEB treated PBMC is 0.083% IFNgamma+ CD8 T cells: LLOQ for SEB treated PBMC is 0.062% LLOQ for CEF treated PBMC is 0.059%	PBMC	Safety set	Cambridge Biomedical Inc.

8.5.2.1 Pharmacokinetic blood collection and handling

Sample(s) will be collected at the time point(s) defined in the assessment schedules below.

Refer to the [\[CCTL019H2301 Laboratory Manual\]](#) for detailed instructions for the collection, numbering, processing, handling, and shipment of PK samples.

Table 8-11 Tisagenlecleucel cellular kinetics by qPCR in peripheral blood collection log for patients in screening to randomization, Arm A, and in patients that cross over from Arm B to Arm A.

Day**	Scheduled Time Point relative to dosing*	Screening to Randomization		Arm A		Cross over from Arm B to Arm A		Sample Volume (ml)
		Dose Reference ID	PK1 Sample No	Dose Reference ID	PK1 Sample No	Dose Reference ID***	PK1 Sample No	
1	D1 Randomization	Pre-dose	-	101	-	-	-	3
1	Unscheduled PK samples ^a	Pre-dose	-	10101	-	-	-	3
1	D22 to D25 Lymphodepleting chemotherapy	Pre-dose	-	-	1	102	-	3
1	D28 (immediately prior to infusion)	D1 (Pre-dose)	-	-	1	103	-	3
1	D28 (10 minutes post-infusion)	D1 (10m post-dose)	-	-	1	104	-	3
1	D29	D2	-	-	1	105	-	3
1	D31±1d	D4	-	-	1	106	2	201
1	D34±1d	D7	-	-	1	107	2	202
1	D38±3d	D11	-	-	1	108	2	203
1	D41±3d	D14	-	-	1	109	2	204
1	D49±3d	D17	-	-	1	110	2	205
1	Week 8±7d	D28	-	-	1	111	2	206
1	Week 12 ±7d	M2	-	-	1	112	2	207
1	M4±14d	M3	-	-	1	113	2	208
1	M6±14d	M5	-	-	1	114	2	209
1	M9±14d	M8	-	-	1	115	2	210
1	M12±14d	M11	-	-	1	116	2	211
1	M18±14d	M17	-	-	1	117	2	212
1	M24±14d	M23	-	-	1	118	2	213
1	M36±14d	M35	-	-	1	119	2	214
1	M48±14d	M47	-	-	1	120	2	215
1	M60±14d	M60	-	-	1	121	2	216
1	Unscheduled PK samples related to CRS ^b	-	-	-	1	10131	2	10201
1	Unscheduled (PK samples related to non-CRS safety events) ^c	-	-	-	1	10151	2	10251
1	Unscheduled (PK samples at relapse) ^d	-	-	-	1	10175	2	10275

Cycle Day**	Scheduled Time Point relative to dosing*	Screening to Randomization		Arm A		Cross over from Arm B to Arm A		
		Dose Reference ID	PK1 Sample No	Dose Reference ID	PK1 Sample No	Dose Reference ID***	PK1 Sample No	Sample Volume (ml)
*Scheduled timepoints are relative to date of tisagenlecleucel infusion, assuming tisagenlecleucel infusion on Day 28 after randomization								
**Additional unscheduled samples may be collected as needed dependent upon individual patient differences in the clinical time-course of CRS, if clinically feasible.								
***The DRID of 2 refers to the first dose received for patients in the cross-over arm and patients will not receive more than one dose of CTL019, this distinguishes the dose reference ID from patients originally randomized to Arm A..								
a. Unscheduled PK samples for Screening to Randomization arm are uniquely, sequentially numbered as 10101, 10102 etc,								
b. Unscheduled PK samples related to a CRS events whereby tocilizumab is not administered are uniquely, sequentially numbered as 10131, 10132 etc. for Arm A; and 10201, 10202 etc, for Cross-over Arm. See Table 8-18 for CTL019 PK collections (qPCR) when tocilizumab is administered during CRS.								
c. Unscheduled anytime PK samples related to other non-CRS safety events will be uniquely, sequentially numbered 10151, 10152 etc. for Arm A and 10251, 10252 etc for Cross-over Arm.								
d. In the event patient relapses, an unscheduled PK sample should be collected along with corresponding immunogenicity sample (refer to Table 8-16 and Table 8-17), and will be uniquely, sequentially numbered 10175, 10176 etc for Arm A and 10275, 10276 for Cross-over Arm.								

Table 8-12 Tisagenlecleucel cellular kinetics by flow cytometry in peripheral blood collection log for patients in screening to randomization, and Arm A, and in patients that cross over from Arm B to Arm A.

Cycle	Day**	Scheduled Time Point relative to dosing*	Screening to Randomization		Arm A		Cross-over from Arm B to Arm A		
			Dose Reference ID	PK2 Sample No	Dose Reference ID	PK2 Sample No	Dose Reference ID***	PK2 Sample No	Sample Volume (ml)
1	D1 Randomization	Pre-dose	-	301	-	-	-	-	2
1	Unscheduled PK samples ^a	Pre-dose	-	10301	-	-	-	-	2
1	D22 to D25 Lymphodepleting chemotherapy	Pre-dose	-	-	1	302	-	-	2
1	D28 (10 minutes post-infusion)	10m post-dose	-	-	1	303	-	-	2
1	D31±1d	D4	-	-	1	304	2	401	2
1	D34±1d	D7	-	-	1	305	2	402	2
1	D38±3d	D11	-	-	1	306	2	403	2
1	D41±3d	D14	-	-	1	307	2	404	2
1	D49±3d	D17	-	-	1	308	2	405	2
1	Week 8±7d	D28	-	-	1	309	2	406	2
1	Week 12 ±7d	M2	-	-	1	310	2	407	2
1	M4±14d	M3	-	-	1	311	2	408	2
1	M6±14d	M5	-	-	1	312	2	409	2
1	M9±14d	M8	-	-	1	313	2	410	2
1	M12±14d	M11	-	-	1	314	2	411	2
1	M18±14d	M17	-	-	1	315	2	412	2
1	Unscheduled PK samples related to CRS ^b		-	-	1	10831	2	10401	2
1	Unscheduled (PK samples related to non-CRS safety events) ^c		-	-	1	10851	2	10451	2
1	Unscheduled (PK samples at relapse) ^d		-	-	1	10875	2	10476	2

Cycle Day**	Scheduled Time Point relative to dosing*	Screening to Randomization		Arm A		Cross-over from Arm B to Arm A		
		Dose Reference ID	PK2 Sample No	Dose Reference ID	PK2 Sample No	Dose Reference ID***	PK2 Sample No	Sample Volume (ml)

* Scheduled timepoints are relative to date of tisagenlecleucel infusion, assuming tisagenlecleucel infusion on Day 28 after randomization

**Additional unscheduled samples may be collected as needed dependent upon individual patient differences in the clinical time-course of CRS, if clinically feasible.

***The DRID of 2 refers to the first dose received for patients in the cross-over arm and patients will not receive more than one dose of CTL019, this distinguishes the dose reference ID from patients originally randomized to Arm A.

^aUnscheduled PK samples for Screening to Randomization arm are uniquely, sequentially numbered as 10301, 10302 etc,

^b. Unscheduled PK samples related to a CRS events whereby tocilizumab is not administered are uniquely, sequentially numbered 10831, 10832 etc.for Arm A and 10401, 10402 etc. for Cross-over arm. See [Table 8-18](#) for CTL019 PK collections (qPCR) when tocilizumab is administered during CRS.

^c. Unscheduled anytime PK samples related to other non-CRS safety events will be uniquely, sequentially numbered 10851, 10852 etc. for Arm A and 10451, 10452 etc. for Cross-over Arm.

^d. In the event patient relapses, an unscheduled PK sample should be collected along with corresponding immunogenicity sample (refer to [Table 8-16](#) and [Table 8-17](#)) and are uniquely and sequentially numbered as 10875, 10876, etc., and 10476, 10477, etc for the Cross-over Arm..

Table 8-13 Tisagenlecleucel cellular kinetics by q-PCR in bone marrow aspirate collection log for patients in screening to randomization, Arm A, and for patients that cross over from Arm B to Arm A.

			Screening to Randomization		Arm A		Cross-over from Arm B to Arm A		
Cycle	Day	Scheduled time point relative to dosing*	PK DRID (CTL019)	PK3 Sample No. (CTL019)	PK DRID (CTL019)	PK3 Sample No. (CTL019)**	PK DRID (CTL019)**	PK3 Sample No. (CTL019)**	Sample Volume (mL)
1	D-14 to D-1 Screening	Pre-dose /screening	-	501	-	-	-	-	3
1	Unscheduled ¹	Pre-dose/ screening	-	10501	-	-	-	-	3
1	Week 8±7d	D28	-	-	1	502	2	601	3
1	M4±14d	M3	-	-	1	503	2	602	3
1	Unscheduled (e.g. at time of radiological CR, related to relapse) ²		-	-	1	10551	2	10601	3

* Scheduled timepoints are relative to date of tisagenlecleucel infusion, assuming tisagenlecleucel infusion on Day 28 after randomization

** Bone Marrow to be collected between Week 8 and M60 only if prior history of BM involvement, as clinically indicated

***The DRID of 2 refers to the first dose received for patients in the cross-over arm and patients will not receive more than one dose of CTL019, this distinguishes the dose reference ID from patients originally randomized to Arm A.

¹Unscheduled PK samples will be uniquely, sequentially numbered 10501, 10502 etc. for patient in Screening to Randomization

² Unscheduled PK samples will be uniquely, sequentially numbered 10551, 10552 etc. for patient in Arm A and 10601, 10602 etc. for patient in Cross-over Arm

Table 8-14 **Tisagenlecleucel cellular kinetics by flow cytometry in bone marrow aspirate collection log for patients in screening to randomization, Arm A, and in patients that cross over from Arm B to Arm A.**

Cycle	Day	Scheduled time point relative to dosing*	Screening to Randomization		Arm A		Cross-over from Arm B to Arm A		Sample Volume (mL)
			PK DRID	PK4 Sample No. (CTL019)	PK DRID	PK4 Sample No. (CTL019)**	PK DRID (CTL019)**	PK4 Sample No. (CTL019)**	
1	D-14 to D-1 Screening	Pre-dose/ screening	-	701	-	-	-	-	2
1	Unscheduled ¹	Pre-dose /screening	-	10701	-	-	-	-	2
1	Week 8±7d	D28	-	-	1	702	2	801	2
1	M4±14d	M3	-	-	1	703	2	802	2
1	Unscheduled (e.g. at time of radiological CR, related to relapse) ²		-	-	1	10721	2	10801	2

* Scheduled timepoints are relative to date of tisagenlecleucel infusion, assuming tisagenlecleucel infusion on Day 28 after randomization

** Bone Marrow to be collected between Week 8 and M60 only if prior history of BM involvement, as clinically indicated

***The DRID of 2 refers to the first dose received for patients in the cross-over arm and patients will not receive more than one dose of CTL019, this distinguishes the dose reference ID from patients originally randomized to Arm A.

¹Unscheduled PK samples will be uniquely, sequentially numbered 10701, 10702 etc. for patient in Screening to Randomization

² Unscheduled PK samples will be uniquely, sequentially numbered 10721, 10722 etc. for patient in Arm A 10801, 10802 etc. for patient in Cross-over Arm

Table 8-15 **Tisagenlecleucel cellular kinetics by q-PCR in CSF biopsy**

To be completed only if CSF collection performed.

Day/ Scheduled Time Point	PK5 Sample No. (CTL)19)	Sample Volume
D-14 to D-1 Screening	901	4-8 mL
Unscheduled (e.g. related to relapse) ¹	10901	4-8 mL

¹Unscheduled PK samples will be uniquely, sequentially numbered 10901, 10902 etc.

Table 8-16 Immunogenicity serum sample collection for patients in screening to randomization, and Arm A, and in patients that cross over from Arm B to Arm A.

		Screening to Randomization	Arm A	Cross over from Arm B to Arm A	Sample volume (mL)
Day/ Scheduled Time Point	Scheduled time point relative to dosing*	IG1 Immunogenicity Sample Number	IG1 Immunogenicity Sample Number	IG1 Immunogenicity Sample Number	
D1 Randomization	Pre-dose	1101	-	-	3
Unscheduled samples ¹	Pre-dose	11151	-	-	3
D27-1d (pre-infusion)	D-1 (Pre-dose)	-	2101	3101	3
D41±3d	D14	-	2102	3102	3
Week 8±7d	D28	-	2103	3103	3
M4±14d	M3	-	2104	3104	3
M6±14d	M5	-	2105	3105	3
M12±14d	M11	-	2106	3106	3
M18±14d	M17	-	2107	3107	3
M24±14d	M23	-	2108	3108	3
M60 ±14d /EOT	M59	-	2109	3109	3
Unscheduled (at relapse)** ²		-	12151	13151	3
Unscheduled (e.g. related to safety events) ³		-	12175	13175	3

* Scheduled timepoints are relative to date of tisagenlecleucel infusion, assuming tisagenlecleucel infusion on Day 28 after randomization

** In the event patient relapses, an unscheduled immunogenicity sample should be collected along with corresponding PK sample (refer to [Table 8-11](#), [Table 8-12](#), [Table 8-13](#), and [Table 8-14](#))

¹Unscheduled immunogenicity samples are uniquely, sequentially numbered 11151, 11152 etc. for Screening to Randomization Arm.

²Unscheduled immunogenicity samples related to a relapse are uniquely, sequentially numbered 12151, 12152 etc. for Arm A and 13151, 13152 etc. for Cross-over arm.

³Unscheduled immunogenicity samples related to safety events will be uniquely, sequentially numbered 12175, 12176 etc. for Arm A and 13175, 13176 etc. for Cross-over Arm.

Table 8-17 Immunogenicity peripheral blood sample collection log for patients in screening to randomization, and Arm A, and in patients that cross over from Arm B to Arm A.

	Scheduled time point relative to dosing*	Screening to Randomization	Arm A	Cross over from Arm B to Arm A	Sample volume (mL)
Day/ Scheduled Time Point		IG2 Immunogenicity Sample Number	IG2 Immunogenicity Sample Number	IG2 Immunogenicity Sample Number	
D1 Randomization	Pre-dose	4101	-	-	6
Unscheduled samples ¹	Pre-dose	14151	-	-	6
D27-1d (pre-infusion)	D-1 Pre-dose	-	5101	6101	6
D41±3d	D14	-	5102	6102	6
Week 8±7d	D28	-	5103	6103	6
M4±14d	M3	-	5104	6104	6
M6±14d	M5	-	5105	6105	6
M12±14d	M11	-	5106	6106	6
M18±14d	M17	-	5107	6107	6
M24±14d	M23	-	5108	6108	6
M60 ±14d /EOT	M59	-	5109	6109	6
Unscheduled (at relapse)**, ²		-	15151	16151	6
Unscheduled (e.g. related to safety events) ³		-	15175	16175	6

* Scheduled timepoints are relative to date of tisagenlecleucel infusion, assuming tisagenlecleucel infusion on Day 28 after randomization

** In the event patient relapses, an unscheduled immunogenicity sample should be collected along with corresponding PK sample (refer to [Table 8-11](#), [Table 8-12](#), [Table 8-13](#), and [Table 8-14](#))

¹Unscheduled immunogenicity samples are uniquely, sequentially numbered 14151, 14152 etc. for Screening to Randomization Arm.

²Unscheduled immunogenicity samples related to a relapse are uniquely, sequentially numbered 15151, 15152 etc. for Arm A and 16151, 16152 etc. for Cross-over arm.

³Unscheduled immunogenicity samples related to safety events will be uniquely, sequentially numbered 15175, 15176 etc. for Arm A and 16175, 16176 etc. for Cross-over Arm.

Table 8-18 Tisagenlecleucel cellular kinetics by qPCR in tocilizumab treated patients during CRS in Arm A and in patients that cross-over from Arm B to Arm A

Day/ Scheduled Time Point**/**	Toci Dose Reference ID	CTL019 Dose Reference ID§	CTL019 PK by qPCR Sample Number^	Sample Volume (whole blood)
D1 (5-15 minutes post infusion)	101	1/2	--	--
D1 1h ± 15 min post infusion	101	1/2	251	2 mL
D2 ± 2h	101	1/2	252	2 mL
D3 ± 4h	101	1/2	253	2 mL
D7 ± 1d	101	1/2	254	2 mL
D1 (pre-dose; second infusion)	101	1/2	255	2 mL
D1(5-15 minutes post second infusion)	102	1/2	--	--
D2 ± 2h from second infusion	102	1/2	256	2 mL
D3 ± 4 hours (post second infusion)	102	1/2	257	2 mL
D7±1d (post second infusion)	102	1/2	258	2 mL
D1 (5-15 minutes pre-dose; additional infusion)	102	1/2	259	2 mL
D1 (5- 15 minutes post additional infusion)	103	1/2	--	--
D2 ± 2 hours	103	1/2	260	2 mL
D3 ± 4 hours	103	1/2	261	2 mL
D7 ± 1d	103	1/2	262	2 mL
Unscheduled***	104,105	1/2	10263, 10264, 10265, 10266	2 mL

* Scheduled timepoints are relative to date of tocilizumab infusion

**Samples may be collected as needed dependent upon administration of tocilizumab, if clinically feasible.

§ For patients in Arm A, the CTL019 dose reference ID will be 1, while for patients in Cross-over Arm, the CTL019 dose reference ID will be 2. Patients in either arm will not receive more than one dose of CTL019. Unscheduled CTL019 cellular kinetics sample collections related to CRS as specified in [Table 8-11](#) will cease once PK sample collections related to tocilizumab administration commence according to Table 8-18, if applicable.

^PK collections for CTL019 measured by qPCR will be numbered starting with 251, 252 etc. series

*** Unscheduled PK samples collected in the event more than 2 tocilizumab doses are administered should follow additional PK collection and numbering schedule (eg. 10263, 10264, etc)..

Rituximab PK will be collected in all patients to determine prior exposure to rituximab therapy. Information regarding prior rituximab therapy (date of last administration, dose etc.) should be recorded on the appropriate CRF page. Rituximab PK samples will be utilized to evaluate the impact of prior rituximab therapy on tisagenlecleucel cellular kinetics.

Table 8-19 Rituximab PK

	Scheduled time point relative to dosing*	Arm A	Arm B	Sample volume (mL)
Day/ Scheduled Time Point		PK7 Sample Number	PK7 Sample Number	
D27-1d (pre-infusion)	D-1 Pre-dose	7101	8101	3
D38±3d	D11	7102	8102	3
M4±14d	M3	7103	8103	3
* Scheduled timepoints are relative to date of tisagenlecleucel infusion, assuming tisagenlecleucel infusion on Day 28 after randomization				

8.5.2.2 Analytical method

All the PK analytes along with the analytical methods and the associated limit of quantification are summarized in [Table 8-10](#).

8.5.3 Biomarkers

Sample(s) will be collected at the time point(s) defined in the assessment schedule.

Follow instructions for sample collection, numbering, processing and shipment provided in the laboratory manual.

Biomarker analyses will focus on:

1. Analysis of the molecular characteristics of baseline, relapsed and progression biopsies and how they correlate with and/or predict clinical response
2. Correlation analysis of biomarker measurements performed pre- and post-infusion with key outcomes of efficacy and safety such as CRS
3. The identification of biomarkers predictive of response to tisagenlecleucel treatment from apheresis product and tisagenlecleucel product in order to support patient selection and guide combination treatments

Analysis of tumor biopsy:

A recent tumor sample obtained for the purpose of the study must be submitted however if not clinically feasible, an archival tumor biopsy from the most recent relapse may be submitted instead. Excisional biopsies should be submitted wherever possible; in cases where this is not possible, a core needle biopsy is allowable. Fine needle aspiration (FNA) is not preferred. Clinical eligibility is based on local histology assessment; however, every effort should be made to submit the tumor biopsy to the central laboratory.

DLBCL sub-typing will be performed by a central laboratory.

Characterization of key biomarkers such as CD19, PD-1 and/or PD-L1, IDO1 on baseline, on treatment and relapsed tumor biopsies will be performed using assays such as immunohistochemistry, immuno-fluorescence, DNA and RNA analysis) as indicated in [Table 8-2](#), [Table 8-4](#), and [Table 8-23](#).

Tumor samples collected in the course of the study may be used for additional exploratory biomarker analysis aiming at identification of potential biomarkers that could be prognostic or predictive of antitumor activity (or lack thereof) to study treatment.

Additional assessments that could be conducted include:

1. Presence/absence and/or localization of immune cells subsets (e.g. T cells, Treg cells, macrophages) in all patients or in specific subset of patients.
2. Expression and/or localization of additional immunohistochemical markers.
3. Tumor samples may be also used for gene expression profiling (e.g. nanostring, RNAseq) to correlate immune signatures or other expression markers with response to treatment.
4. Sequencing of specific genes, or whole exome sequencing. This analysis will explore the presence of oncogenic drivers and their impact on antitumor activity of the study treatment. The sequencing data may also be used to explore the mutational load and neoantigenic potential of the tumor cells

Soluble immune markers:

The serum levels of inflammatory cytokines and other soluble factors will be assessed pre- and post- tisagenlecleucel administration. These data will be used in order to attempt to retrospectively identify candidate serum markers potentially correlated with tisagenlecleucel efficacy, CRS severity and possible CNS toxicity.

Peripheral blood:

The effect of tisagenlecleucel therapy on B and T cell levels will be measured in peripheral blood to assess on-target effect on these CD19 positive cells.

Peripheral blood leukocytes characterization will include immunophenotyping and T cell subset analysis, and may also include transcriptome analysis and single nucleotide polymorphism (SNP) analysis. Comprehensive DNA sequencing is within scope of these analyses (in accordance with local regulations); at a minimum, targeted sequencing of genes relevant to the tisagenlecleucel mechanism of action will be conducted.

Analysis of peripheral blood leukocyte characteristics will be performed to identify potential markers associated with tisagenlecleucel efficacy, expansion and safety. The correlation between characteristics of tisagenlecleucel cell product and apheresis product with PK parameters, clinical efficacy and safety endpoints will also be explored.

Composition of T cell subsets and cell lineages in peripheral blood and apheresis product with progressive disease may also be assessed.

Minimal Residual Disease and tumor evolution:

Immunoglobulin (Ig) deep sequencing may be performed on bone marrow, whole blood, tumor or circulating tumor DNA when available, to identify prognostic and predictive value of minimal residual disease (MRD) and tumor clonality evolution. These analyses will be conducted at baseline, on-study samples and sample collected at relapse and progression.

Table 8-20 Biomarker sample collection- peripheral blood for serum cytokine and soluble marker analyses

Day/ Scheduled Time Point*	Patients receiving the tisagenlecleucel (Arm A, or cross-over patients)	Arm B
D1 Randomization	5 mL	5 mL
D22-D25 Lymphodepletion Chemotherapy	5 mL	
D27 Pre-tisagenlecleucel infusion	5 mL	
D29	5 mL	
D31±1d	5 mL	
D34±1d	5 mL	
D38±3d	5 mL	
D41±3d	5 mL	
D49±3d	5 mL	
Week 8±7d	5 mL	
Week 12±7d	5 mL	
M6±14d	5 mL	
M12±14d	5 mL	
Unscheduled (samples related to CRS, samples related to relapse or safety events),	5mL	
* All measurement times are relative to date of randomization unless otherwise specified.		

Table 8-21 Biomarker sample collection – B cell levels (peripheral blood)

Day/ Scheduled Time Point*	Patients receiving the tisagenlecleucel (Arm A, or cross-over patients)	Arm B
D1 Randomization	5 mL	5 mL
D22-D5 LD	5 mL	
D27 Pre-tisagenlecleucel infusion	5 mL	
D34±1d	5 mL	5 mL
D38±3d	5 mL	
D41±3d	5 mL	
Week 12±7d	5 mL	5 mL
M6±14d	5 mL	5 mL
M12±14d	5 mL	5 mL
M18±14d	5 mL	5 mL
M24±14d	5 mL	5 mL
M36±14d	5 mL	5 mL
M48±14d	5 mL	5 mL
M60 ±14d End of Treatment and Follow-up	5 mL	5 mL
Unscheduled (e.g. related to relapse)	5 mL	5 mL
* All measurement times are relative to date of randomization unless otherwise specified.		

Table 8-22 Biomarker sample collection – immunophenotyping, gene expression profiling, (peripheral blood) and ctDNA plasma for MRD and tumor clonal analysis by Ig deep sequencing

Day/ Scheduled Time Point*	Patients receiving the tisagenlecleucel (Arm A, or cross-over patients)	Arm B
D1 Randomization	12.5 mL	12.5 mL
D22-D25 (D1-D5 for PD arm) Lymphodepletion Chemotherapy	12.5 mL	
D27 Pre-tisagenlecleucel infusion	12.5 mL	
D34±1d	12.5 mL	
D38±3d	12.5 mL	
Week 8±7d	12.5 mL	
Week 12±7d	12.5 mL	
M6±14d	12.5 mL	
M9±14d	12.5 mL	
M12±14d	12.5 mL	
M18±14d	12.5 mL	
M24±14d	12.5 mL	
M36±14d	12.5 mL	
M48±14d	12.5 mL	
M60±14d End of Treatment and Follow-up	12.5 mL	
q3M Survival Follow-up	12.5 mL	
Unscheduled (e.g. related to relapse)	12.5 mL	
Peripheral blood before leukapheresis (Flow cytometry)		
D-14 to D-1 Screening	6 mL	
Leukapheresis product (Flow Cytometry)		
D-14 to D-1 Screening	2 mL	
* All measurement times are relative to date of randomization unless otherwise specified.		

Table 8-23 Sample collection - exploratory analysis on tumor biopsy

Mandatory, if accessible and does not impact treatment

Day/Scheduled Time Point*	Sample Number	Arm A or cross-over patients	Arm B
D-14 to D-1 Screening**	11301	X	X
D35-D49	11302	X	
M4	11303	X	
***Unscheduled at relapse or progression in patients following CTL019 infusion (or as clinically indicated), and if available post-mortem from autopsy material following relapse or progression	11351	X	
*All measurement times are relative to date of randomization unless otherwise specified. **A FFPE tumor biopsy is needed at screening for diagnosis confirmation ***Unscheduled collection related to relapse or progression: a FFPE tumor biopsy (excisional or core needle) is mandatory if accessible and does not impact treatment. A FFPE tumor biopsy (excisional or core needle) as clinically indicated should be submitted if PET-CT shows residual metabolically active tumor tissue.			

8.5.3.1 Optional additional biomarker studies using remaining samples

If the patient agrees, the remaining biomarker and/or PK samples as well as any remaining tisagenlecleucel product may be stored for up to 15 years and further analyzed to address scientific questions related to tisagenlecleucel or cancer or for studies related to improvements in the manufacturing process. A decision to perform such additional research studies would be based on outcome data from this study or from new scientific findings related to the drug class or disease, as well as reagent and assay availability.

8.5.4 Imaging

The methods for assessment and recording are specified in the imaging charter.

The coded medical images will be used primarily for analysis as described in this protocol; however, the images may also be used for the development and evaluation of new analysis methods directly related to the area of research that this study covers.

8.5.5 Survival follow-up

For all randomized patients, follow-up for survival every 3 months until the end of study (defined as the last visit for the last patient randomized). If a patient misses a quarterly scheduled visit where survival status is required, or if the time-point does not align with a scheduled visit, survival status can be obtained via phone contact. For example, if regularly scheduled visits occur within 3 months of each other, no specific survival contact is needed. However, if the patient misses a visit, or if the visit is not scheduled for longer than 3 months, survival status may be collected via phone contact and should be entered on the appropriate CRF.

8.5.6 Other assessments

No additional tests will be performed on subjects entered into this study.

9 Study discontinuation and completion

9.1 Discontinuation

9.1.1 Discontinuation of study treatment

The investigator must discontinue study treatment for a given subject if, he/she believes that continuation would negatively impact the subject's well-being.

A single tisagenlecleucel infusion may be discontinued if, in the investigator's opinion, its continuation would be detrimental to the patient's safety.

For patients randomized to Arm B (SOC) arm or patients who never receive tisagenlecleucel in Arm A, study treatment includes multiple lines of salvage immunochemotherapy as per local practice. Discontinuation of study treatment for a patient occurs when this study treatment is stopped earlier than the planned duration according to local guidelines and the approved drug label, and can be initiated by either the patient or the investigator.

Regardless of treatment arm, patients who discontinue from treatment and follow up should NOT be considered withdrawn from the study before they return for the safety follow-up visit and the End-of-Study (EOS) assessments indicated in [Section 9.2](#). If they fail to return for these assessments, every effort (e.g. telephone, email, letter) should be made to contact them.

Study treatment must be discontinued under the following circumstances

- Subject/guardian decision
- Pregnancy
- Use of prohibited treatment as per recommendations in the prohibited treatment section
- Any situation in which study participation might result in a safety risk to the subject
- Any AEs that in the judgment of the investigator, prevents the patient from continuing study treatment”
- Any laboratory abnormalities that in the judgment of the investigator, prevents the patient from continuing study treatment

If discontinuation of study treatment occurs, the investigator should make a reasonable effort to understand the primary reason for the subject’s premature discontinuation of study treatment and record this information.

Subjects who discontinue study treatment or who decide they do not wish to participate in the study further should NOT be considered withdrawn from the study UNLESS they withdraw their consent (see withdraw of informed consent section). **Where possible, they should return for the assessments indicated** in the assessment schedule. If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone, e-mail, letter) should be made to contact the subject/pre-designated contact as specified in the lost to follow-up [Section 9.1.4](#). This contact should preferably be done according to the study visit schedule.

If the subject cannot or is unwilling to attend any visit(s), the site staff should maintain regular telephone contact with the subject, or with a person pre-designated by the subject. This telephone contact should preferably be done according to the study visit schedule.

After study treatment discontinuation, at a minimum, in abbreviated visits, the following data should be collected at clinic visits or via telephone/email contact:

- new / concomitant treatments
- adverse events/Serious Adverse Events

The investigator must also contact the IRT to register the subject’s discontinuation from study treatment.

For patients who discontinue treatment for reasons other than documented disease progression, death, lost to follow-up, or withdrawal of consent, tumor assessments must continue to be performed as per the visit evaluation schedule until documented disease progression per BIRC, death, lost to follow-up, or withdrawal of consent.

9.1.2 Criteria for premature patient discontinuation from the study

Patients must be followed according to the visit schedule to ensure adequate data are collected for the proper assessment of study primary and secondary objectives.

All patients who receive tisagenlecleucel should be kept on study until the Month 60 visit whenever possible. It is anticipated that patients who received tisagenlecleucel treatment may discontinue from the efficacy portion of the study due to BIRC-confirmed disease PD/SD and only require the collection of key safety data in the long term additional follow-up. In cases where a patient discontinues without BIRC confirmed PD/SD, it may be possible for the patient to be followed for key safety follow-up only after consultation and documented agreement with the Novartis medical monitor.

After 5 years of follow-up, patients will be asked to join the separate long term follow-up study (CTL019A2205B). If patients move to the long term follow-up study, survival status should still be collected in this study until the end of study, defined as the last visit for the last patient randomized. The appropriate disposition eCRF should be recorded when the patient moves into the long term additional follow-up and if the patient withdraws from the study prematurely.

Patients may voluntarily withdraw from the study or be withdrawn from the study at the discretion of the investigator at any time. Patients may also request to only be followed for survival at any time.

Patients may be withdrawn from the study if any of the following occur:

- The patient is lost to follow-up
- Patient noncompliance with study therapy and/or clinic appointments
- Voluntary withdrawal; a patient may remove himself/herself from the study at any time without prejudice.
- Termination of the study by the sponsor or the health authorities

9.1.3 Withdrawal of informed consent

Subjects may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs only when a subject:

- Does not want to participate in the study anymore, and
- Does not allow further collection of personal data

In this situation, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for the subject's decision to withdraw his/her consent and record this information. Study treatment must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

Further attempts to contact the subject are not allowed unless safety findings require communicating or follow-up. All efforts should be made to complete the assessments prior to study withdrawal. A final evaluation at the time of the subject's study withdrawal should be made as detailed in the assessment table.

Novartis will continue to keep and use collected study information (including any data resulting from the analysis of a subject's samples until their time of withdrawal) according to applicable law.

For US and Japan: All biological samples not yet analyzed at the time of withdrawal may still be used for further testing/analysis in accordance with the terms of this protocol and of the informed consent form.

For EU and RoW: All biological samples not yet analyzed at the time of withdrawal will no longer be used, unless permitted by applicable law. They will be stored according to applicable legal requirements.

9.1.4 Lost to follow-up

For subjects whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator must show "due diligence" by documenting in the source documents steps taken to contact the subject, e.g. dates of telephone calls, registered letters, etc. A subject should not be considered as lost to follow-up until due diligence has been completed **or until the end of the study**.

9.1.5 Early study termination by the sponsor

The study can be terminated by Novartis at any time for any reason. This may include reasons related to the benefit/ risk assessment of participating in the study, practical reasons (including slow enrollment), or for regulatory or medical reasons. In taking the decision to terminate, Novartis will always consider the subject welfare and safety. Should early termination be necessary, subjects must be seen as soon as possible (provide instruction for contacting the subject, when the subject should stop taking drug, when the subject should come for a final visit) and the same assessments should be performed as described in [Section 8](#) for a discontinued or withdrawn subject. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the subject's interests. For subjects who have received a tisagenlecleucel infusion, a long term post-study follow-up for lentiviral vector safety will still continue under a separate destination protocol for 15 years post infusion per health authority guidelines. The investigator or sponsor depending on the local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

9.1.6 Criteria for stopping or pausing the study

The study will be paused, and health authorities notified if:

- Any subject develops detectable replication competent lentivirus (RCL) during the study
- The Sponsor, DMC (if applicable), or any regulatory body decides for any reason that subject safety may be compromised by continuing the study
- The Sponsor decides to discontinue the development of the intervention to be used in this study

The study may be paused pending notification of the health authorities and the DMC for investigation and possible protocol amendment if any subject experiences any of the following events within three weeks of the tisagenlecleucel cell infusion and re-infusion:

- Life-threatening (grade 4) toxicity attributable to protocol therapy that is unmanageable, unexpected and unrelated to chemotherapy and attributable to protocol therapy. High fevers, hypotension, hypoxia, disseminated intravascular coagulation, encephalopathy (e.g.

lethargy, confusion, aphasia, seizure), ICU admission, dialysis and mechanical ventilation are expected. The expected side effects can also result in grade 4 liver toxicity, nephrotoxicity and cardiac dysfunction.

- Death suspected to be related to tisagenlecleucel therapy

9.2 Study completion and post-study treatment

The end of study is when all subjects have completed Month 60/EOS evaluation or were withdrawn prematurely, and any repeat assessments associated with this visit have been documented and followed-up appropriately by the Investigator, or in the event of an early study termination decision, the date of that decision. Subjects who have completed their Month 60/EOS visit before the end of the study (defined as the last visit for the last patient randomized) will be followed every 3 months (q3m) until the end of the study for survival information, and will also be asked to join the separate LTFU study (CTL019A2205B).

The primary analysis will occur when approximately 200 of EFS events is reached. At this time, the primary clinical study report (CSR) will be produced. After the primary analysis of EFS, the study will remain open provided the EFS demonstrates treatment benefit. Subjects still being followed on the study after the primary analysis time point will continue as per the schedule of assessments. The study will end once the final OS analysis is performed when statistical significance is reached for OS analysis, see the statistical model, hypothesis, and method of analysis section) and the final analysis of study data is conducted. All available data from all subjects up to this cutoff date will be analyzed. At the end of the study, every effort will be made to continue provision of study treatment outside this study through an alternative setting to subjects who in the opinion of the Investigator are still deriving clinical benefit. If the primary analysis of EFS does not demonstrate treatment benefit, the follow-up for OS will end.

All randomized patients should have a safety follow-up visit conducted 8 weeks after their last treatment administration or prior to starting another anticancer therapy, whichever occurs first. The information collected is kept as source documentation. All SAEs reported during this time period must be reported as described in [Section 10.1.3](#). Patients should continue to be followed under the current protocol for key safety and survival, as per the long term additional follow-up schedule in [Table 8-2](#) and [Table 8-4](#). Survival assessments can be conducted via a form or telephone contact until last patient last visit (LPLV) as defined above.

In addition, semiannual and annual evaluations will be performed for up to 15 years from the date of tisagenlecleucel infusion on all subjects. Patients should be followed for the first 5 years on this protocol and an additional 10 years under a separate long term follow-up (LTFU) protocol as recommended by health authority guidance for subjects treated with gene therapies. Patients who receive tisagenlecleucel will be asked to join a separate long term follow up study [CTL019A2205B].

At the time of the end of this study (defined as the last visit for the last patient randomized), subjects continuing to derive benefit from the comparator treatment in the opinion of the Investigator may continue such treatment at the investigators discretion according to local clinical practice.

10 Safety monitoring and reporting

10.1 Definition of adverse events and reporting requirements

10.1.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (e.g., any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a subject or clinical investigation subject after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the infusion of tisagenlecleucel.

The investigator has the responsibility for managing the safety of individual subject and identifying adverse events.

Novartis qualified medical personnel will be readily available to advise on trial related medical questions or problems.

The occurrence of AEs must be sought by non-directive questioning of the subject at each visit during the study. Adverse events also may be detected when they are volunteered by the subject during or between visits or through physical examination findings, laboratory test findings, or other assessments.

Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate Adverse Event.

Adverse events must be recorded under the signs, symptoms or diagnosis associated with them, accompanied by the following information (as far as possible) (if the event is serious refer to [Section 10.1.2](#)):

1. Adverse events will be assessed and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5, with the exception of CRS, which will follow [Table 6-2](#) and [Table 6-3](#). If CTCAE grading does not exist for an AE, the severity of mild, moderate, severe, life-threatening and fatal, corresponding to Grades 1 - 5, will be used.
2. its relationship to the study treatment and other investigational treatment If the event is due to lack of efficacy or progression of underlying illness (i.e. progression of the study indication) the assessment of causality will usually be 'Not suspected'. The rationale for this guidance is that the symptoms of a lack of efficacy or progression of underlying illness are not caused by the trial drug, they happen in spite of its administration and/or both lack of efficacy and progression of underlying disease can only be evaluated meaningfully by an analysis of cohorts, not on a single subject.
3. its duration (start and end dates) or if the event is ongoing, an outcome of not recovered/not resolved must be reported.
4. whether it constitutes a serious adverse events (SAE) (see [Section 10.1.2](#) for definition of SAE) and which seriousness criteria have been met.

5. action taken regarding with study treatment.
All adverse events must be treated appropriately. Treatment may include treatment interruption or withdrawal.
6. its outcome, i.e., its recovery status or whether it was fatal.

If the event worsens the event should be reported a second time in the eCRF noting the start date when the event worsens in toxicity. For grade 3 and 4 AEs only, if improvement to a lower grade is determined a new entry for this event should be reported in the eCRF noting the start date when the event improved from having been Grade 3 or Grade 4.

Conditions that were already present at the time of informed consent should be recorded in medical history eCRF.

Adverse events (including laboratory abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms.

Adverse event monitoring should be continued for the duration as specified in [Section 10.1.1](#).

Once an AE is detected, it must be followed until its resolution or until it is judged to be permanent (e.g., continuing at the end of the study), and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study treatment, the interventions required to treat it, and the outcome.

Progression of malignancy (including fatal outcomes), if documented as per [\[Lugano guideline\]](#) should not be reported as a SAE.

Adverse events separate from the progression of malignancy (e.g., deep vein thrombosis at the time of progression or hemoptysis concurrent with finding of disease progression) will be reported as per usual guidelines used for such events with proper attribution regarding relatedness to the treatment.

Information about adverse drug reactions for the investigational drug can be found in the [Tisagenlecleucel Investigator's Brochure].

Abnormal laboratory values or test results constitute AEs only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms
- they are considered clinically significant
- they require therapy

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in subjects with the underlying disease.

Detailed guidance to determine whether or not a non-serious AE, an SAE, concomitant medication, or laboratory result has to be recorded in the eCRF during the relevant study period is provided in [Section 16.3](#) Appendix 3.

10.1.1.1 Duration of adverse event reporting

10.1.1.1.1 Adverse event reporting for patients from ICF through safety follow-up visit

The safety follow-up visit should occur 8 weeks after last treatment administration or prior to starting new anticancer therapy, whichever occurs first. From the time of ICF to the safety follow-up visit, all new or worsening AEs (including laboratory abnormalities deemed clinically significant by the investigator), regardless of causality will be recorded in the Adverse Events eCRF. Any event which started prior to the safety follow-up visit and is ongoing at the time of the visit should continue to be followed until resolution. The primary safety analysis will occur using only those events which occur during this time period for both arms.

10.1.1.1.2 Adverse event reporting following the safety follow-up visit until Month 60 (only patients who receive tisagenlecleucel)

The safety follow-up visit should occur 8 weeks after last treatment administration or prior to starting new anticancer therapy, whichever occurs first. After this visit, adverse events are no longer reportable for patients who do not receive tisagenlecleucel.

For patients who receive tisagenlecleucel, the collection of certain select adverse events is required to monitor for long term effects of therapy. Following this visit and through Month 60 or premature discontinuation from the trial, AEs should only be recorded in the Adverse Events eCRF if they meet one of the criteria:

- Events leading to death
- Serious or opportunistic infections. Defined as bacterial, viral, fungal or parasitic infections that fulfill one of the following criteria:
 - Require anti-infective treatment OR
 - Lead to significant disability or hospitalization OR
 - Need for surgical or other intervention
- New incidence or exacerbation of a pre-existing neurologic disorder
- New incidence or exacerbation of a prior rheumatologic or other autoimmune disorder
- New incidence of other hematologic disorder
- Any severe AE or condition the treating physician believes may have a reasonable relationship to tisagenlecleucel therapy or study procedures
- Positive RCL test
- Vector insertion site sequencing result with a mono-or oligoclonality pattern or in a location near a known human oncogene
- Secondary malignancies, i.e. new malignancy (e.g. T-cell and non T-cell hematological malignancies, solid organ malignancies), other than the primary malignancy
- Progressive multifocal leukoencephalopathy (PML)
- Hepatitis B reactivation

These AEs must be collected and recorded in the study database, irrespective of causal association. Adverse events (including laboratory abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate AE.

10.1.1.1.3 Adverse event reporting following Month 60 through completion of 15 years post tisagenlecleucel infusion

Following the Month 60 visit, any AEs experienced should only be reported to Novartis, if the treating physician suspects a causal relationship to tisagenlecleucel. However, the following events should be reported to Novartis regardless of causality:

- New incidence or exacerbation of a pre-existing neurologic disorder
- New incidence or exacerbation of a prior rheumatologic or other autoimmune disorder
- New incidence of other hematologic disorder
- Secondary malignancies, i.e. new malignancy (e.g. T-cell and non T-cell hematological malignancies, solid organ malignancies), other than the primary malignancy. These AEs must be collected and recorded in the study database.

10.1.1.1.4 Adverse events of special reporting requirements

If specifically requested by a local Health Authority, expedited reporting of pre-specified AEs will occur.

10.1.2 Serious adverse events

An SAE is defined as any AE (appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s) or medical condition(s) which meets any one of the following criteria:

- fatal
- life-threatening

Life-threatening in the context of a SAE refers to a reaction in which the subject was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (please refer to the ICH-E2D Guidelines).

- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
 - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
 - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
 - social reasons and respite care in the absence of any deterioration in the subject's general condition

- treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
- is medically significant, e.g. defined as an event that jeopardizes the subject or may require medical or surgical intervention to prevent one of the outcomes listed above

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the subject or might require intervention to prevent one of the other outcomes listed above. Such events should be considered as “medically significant”. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse.

All malignant neoplasms will be assessed as serious under “medically significant” if other seriousness criteria are not met and the malignant neoplasm is not a disease progression of the study indication.

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

All reports of intentional misuse and abuse of the product are also considered serious adverse event irrespective if a clinical event has occurred

10.1.3 SAE reporting

To ensure subject safety, every SAE, regardless of causality, occurring after the subject has provided informed consent to Novartis safety within 24 hours of learning of its occurrence. The duration of this SAE reporting requirement is outlined in [Section 10.1.1.1](#). Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site.

1. Screen Failures (e.g. A subject who is screened but is not treated or randomized)

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

If the SAE is not previously documented in the Investigator’s Brochure or Package Insert (new occurrence) and is thought to be related to the study treatment, a CMO&PS Department associate may urgently require further information from the investigator for health authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same study treatment that this SAE has been reported.

Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

SAEs will only be reported if the event is suspected to be causally related to a study procedure as assessed by the investigator (e.g. an invasive procedure such as biopsy). SAEs will be followed until resolution or until clinically relevant improvement or stabilization. SAE collection ends 30 days after the last study related procedure. Any SAEs experienced after the 30 day period should only be reported to Novartis Safety if the investigator suspects a causal relationship to study treatment.

10.1.4 Pregnancy reporting

Pregnancies

To ensure subject safety, each pregnancy occurring after signing the informed consent must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded and reported by the investigator to the Novartis Chief Medical Office and Patient Safety (CMO&PS). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to tisagenlecleucel infusion any pregnancy outcome. Any SAE experienced during pregnancy must be reported.

Pregnancy outcomes should be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

Pregnancy outcomes should be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

10.1.5 Reporting of study treatment errors

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, subject or consumer (European Medicines Agency (EMA) definition).

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol.

Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

Study treatment errors and uses outside of what is foreseen in the protocol will be recorded on the appropriate CRF irrespective of whether or not associated with an AE/SAE and reported to Safety only if associated with an SAE.

Table 10-1 Guidance for capturing the study treatment errors including misuse/abuse

Treatment error type	Document in Dosing CRF (Yes/No)	Document in AE eCRF	Complete SAE form
Unintentional study treatment error	Yes	Only if associated with an AE	Only if associated with an SAE

For more information on AE and SAE definition and reporting requirements, please see the, respective sections.

10.2 Additional safety monitoring

10.2.1 Liver safety monitoring

To ensure subject safety and enhance reliability in determining the hepatotoxic potential of tisagenlecleucel, a standardized process for identification, monitoring and evaluation of liver events has to be followed.

The following two categories of abnormalities / adverse events have to be considered during the course of the study (irrespective of whether classified/reported as AE/SAE):

- Liver laboratory triggers, which will require repeated assessments of the abnormal laboratory parameter
- Liver events, which will require close observation, follow-up monitoring and contributing factors are recorded on the appropriate CRFs

Please refer to [Table 16-3](#) in [Section 16.4](#) for complete definitions of liver laboratory triggers and liver events.

Every liver event defined in [Table 16-3](#) should be followed up by the investigator or designated personnel at the trial site, as summarized below. Additional details on actions required in case of liver events are outlined in [Table 16-4](#). Repeat liver chemistry tests (ALT, AST, TBILI, PT/INR, ALP and gamma glutanyl transferase (GGT)) to confirm elevation.

- These liver chemistry repeats will be performed using the central laboratory. If results will not be available from the central laboratory, then the repeats can also be performed at a local laboratory to monitor the safety of the subject. If a liver event is subsequently reported, any local liver chemistry tests previously conducted that are associated with this event should have results recorded on the appropriate CRF

If the initial elevation is confirmed, close observation of the subject will be initiated, including consideration of treatment interruption if deemed appropriate.

- Discontinuation of the investigational drug (refer to the Discontinuation of study treatment [Section 9.1.1](#)), if appropriate
- Hospitalization of the subject if appropriate
- Causality assessment of the liver event
- Thorough follow-up of the liver event, which can include based on investigator's discretion:
 - Serology tests, imaging (e.g., such as abdominal ultrasound (US), CT or MRI, as appropriate) and pathology assessments, gastroenterologist's or hepatologist's

consultancy; obtaining more detailed history of symptoms and prior or concurrent diseases, history of concomitant drug use, exclusion of underlying liver disease, obtaining a history of exposure to environmental chemical agents.

All follow-up information, and the procedures performed must be recorded as appropriate in the CRF.

10.2.2 Renal safety monitoring

The following two categories of abnormal renal laboratory values have to be considered during the course of the study:

- Serum creatinine increase $\geq 25\%$ compared to baseline during normal hydration status
- Urine protein-creatinine ratio (PCR) $\geq 1\text{g/g}$ or $\geq 100\text{ mg/mmol}$, OR new onset dipstick proteinuria $\geq 3+$ OR new onset dipstick hematuria $\geq 3+$ (after excluding menstruation, urinary tract infection, extreme exercise, or trauma)

Renal event findings must be confirmed 24-48 hours after the first assessment (*select as applicable*: for Phase 1 and early Phase 2) OR after ≥ 24 hours but ≤ 5 days after first assessment (*select as applicable*: for Phase 2 and Phase 3).

Every renal laboratory trigger or renal event as defined in [Table 16-10](#) should be followed up by the investigator or designated personnel at the trial site as summarized in [Table 16-11](#).

10.2.3 Data Monitoring Committee

This study will include a data monitoring committee (DMC) which will function independently of all other individuals associated with the conduct of this clinical trial, including the site investigators participating in the study. The DMC will assess at defined intervals the progress of a clinical trial, safety data, and critical efficacy variables and recommend to the sponsor whether to continue, modify or terminate a trial.

Specific details regarding composition, responsibilities, data monitoring and meeting frequency, and documentation of DMC reports, minutes, and recommendations will be described in a separate charter that is established between the sponsor and the DMC.

10.2.4 Steering committee

The steering committee (SC) will be established comprising investigators participating in the trial, Novartis representatives from the Clinical Trial team and not members of the DMC. The SC will ensure transparent management of the study according to the protocol through recommending and approving modifications as circumstances require. The SC will review protocol amendments as appropriate. Together with the clinical trial team, the SC will also develop recommendations for publications of study results including authorship rules. The details of the role of the Steering Committee will be defined in a Steering Committee charter.

10.2.5 Blinded independent review committee (BIRC)

A BIRC will be established to review data related to disease response assessments during the study, before randomization and determine response and relapse for the primary analysis. A BIRC charter will detail the BIRC data flow and review process in alignment with the

response definitions in [Section 16.2](#) Appendix 2. Patient management will be based upon local investigator assessments except for the eligibility crossover. The designation of response and relapse for the primary analysis and other related secondary efficacy endpoints will be based on the evaluations made by the BIRC. Details regarding the constitution of the BIRC and its specific roles will be documented in the BIRC charter and agreed upon between Novartis and the BIRC before initiation of any BIRC review.

10.2.6 Follow up of secondary malignancy

For patients treated with tisagenlecleucel, treating physician/ healthcare providers should contact Novartis if the patient develops a secondary malignancy. Upon clinical confirmation secondary malignancy, blood samples should be collected for cellular kinetic analysis by qPCR and flow cytometry. Two tubes of blood are requested: 10 ml sample of peripheral blood mononuclear cells (PBMCs) in a sodium heparin collection tube and 6 ml of blood in ethylenediaminetetraacetic acid (EDTA) tube. Novartis strongly recommends collection of biopsy samples from secondary malignancies for exploratory analysis. Additional details for sample handling and shipping are outlined in the laboratory manual.

11 Data collection and database management

11.1 Data collection

Designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRF). The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements. Investigator site staff will not be given access to the electronic data capture (EDC) system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs, allow modification and/or verification of the entered data by the investigator staff.

The investigator/designee is responsible for assuring that the data (recorded on CRFs) (entered into eCRF) is complete, accurate, and that entry and updates are performed in a timely manner. The Investigator must certify that the data entered are complete and accurate

After final database lock, the investigator will receive copies of the subject data for archiving at the investigational site.

All data should be recorded, handled and stored in a way that allows its accurate reporting, interpretation and verification.

11.2 Database management and quality control

Novartis personnel (or designated CRO) will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.

Concomitant treatments and prior medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical (ATC)

classification system. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Randomization codes will be tracked using an Interactive Response Technology (IRT). The system will be supplied by a vendor, who will also manage the database. The data will be sent electronically to Novartis at specific timelines.

Once all the necessary actions have been completed and the database has been declared to be complete and accurate, it will be locked. Any changes to the database after that time can only be made after written agreement by Novartis development management.

11.3 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and data capture requirements (i.e. eSource DDE or eCRFs) with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of subject records, the accuracy of data capture / data entry, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized Novartis/ CRA organization. Additionally, a central analytics organization may analyze data & identify risks & trends for site operational parameters, and provide reports to Novartis clinical teams to assist with trial oversight.

The investigator must maintain source documents for each subject in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the subject's file. The investigator must also keep the original informed consent form signed by the subject (a signed copy is given to the subject).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, adherence to PRO assessment, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the subjects will be disclosed.

12 Data analysis and statistical methods

It is planned that the data from all centers participating in the trial will be combined, so that an adequate number of patients are available for analysis. Novartis and/or a designated CRO will perform the final EFS analyses. Any data analyses performed independently by any investigator should be submitted to Novartis before publication or presentation.

The primary efficacy and safety analyses will be performed after observing approximately 200 EFS events have been documented by BIRC. Following the primary analysis for EFS, the study will remain open. Patients still being followed on the study will continue as per the schedule of assessments.

The study will end once the final OS analysis is performed at approximately 5 years from the 1st patient randomized to the study, or earlier, if statistical significance is reached at the interim analysis for OS at the time of the primary analysis of EFS, at which point the final CSR will be published. All available OS and safety data from all patients up to this cutoff date will be analyzed.

Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

12.1 Analysis sets

The analysis sets to be used are defined as below. The Full Analysis Set (FAS) will be used as the main analysis set for efficacy, demographics and other baseline characteristics. The Safety Set will be used for all the safety analysis. The Pharmacokinetic Analysis Set (PAS) will be used for the cellular kinetics analysis.

12.1.1 Screened Set

The Screened Set comprises all patients who have signed informed consent and screened in the study.

12.1.2 Full Analysis Set

The Full Analysis Set (FAS) comprises all patients to whom study treatment has been assigned by randomization. According to the intent to treat principle, patients will be analyzed according to the treatment and strata they have been assigned to during the randomization procedure.

12.1.3 Safety Set

The Safety Set includes all randomized patients who received at least one dose of any component of study treatment. Patients will be analyzed according to randomized treatment.

12.1.4 Per-Protocol Set

The Per-Protocol Set (PPS) consists of a subset of patients in the FAS who are compliant with requirements of the clinical study protocol (CSP).

Protocol deviations leading to exclusion from the PPS include:

- Diagnosis of disease other than histologically confirmed, aggressive B-cell NHL at relapse /progression after front line therapy (inclusion 2);

The detailed exclusion criteria of PPS will be determined and documented in the study Report and Analysis Plan (RAP)

12.1.5 Pharmacokinetic analysis set

The tisagenlecleucel cellular kinetic analysis set (CKAS) consists of patients in FAS who have received one dose of tisagenlecleucel and have at least one evaluable cellular kinetic parameter. The CKAS will be used for summaries (tables and figures) of cellular kinetic data.

The tocilizumab pharmacokinetic analysis set (TPAS) consists of all patients who have taken at least one dose of tocilizumab and provided at least one tocilizumab PK concentration.

12.2 Subject demographics and other baseline characteristics

Demographic and other baseline data will be listed and summarized descriptively by treatment arm for the FAS.

Categorical data will be presented as frequencies and percentages. For continuous data, summary statistics will be presented (i.e., including mean, standard deviation, median, minimum, and maximum). For selected parameters, 25th and 75th percentiles will also be presented.

Relevant medical histories and current medical conditions at baseline will be summarized by system organ class and preferred term, by treatment arm. Number and percentage of patients who received prior anti-neoplastic medications/therapies will be summarized. Patients will be classified by their prior treatment response.

12.3 Treatments

The Safety set will be used for the analyses below. Categorical data will be summarized as frequencies and percentages. For continuous data, mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum will be presented.

For patients who received tisagenlecleucel infusion, the total cells infused (cells) and total tisagenlecleucel transduced viable T cells infused (cells) will be listed and summarized using descriptive statistics. Patients will be categorized as below, within or above the prescribed dose range.

For patients who received standard of care therapy, the medication name, length of therapy and total dose will be listed and summarized using descriptive statistics.

Concomitant medications and significant non-drug therapies prior to and after the start of CTL infusion or SOC treatment(s) will be listed by patient and summarized by the Anatomical Therapeutic Chemical (ATC) term classification system, by treatment arm. Lymphodepleting chemotherapies will be listed and summarized. Transfusion during the study will be listed. In addition, anti-cytokine medications for the management of CRS will be summarized.

12.4 Analysis of the primary endpoint(s)

The primary aim of the study is to compare two second line treatment strategies in adult patients with aggressive B-cell non-Hodgkin lymphoma who are refractory to or relapsed after frontline standard of care and are eligible for stem cell transplantation. The treatment strategies will be compared based on their effect on delaying the composite event of disease

progression / stable disease at the week 12 (± 1 week) assessment or death at any time. These two treatment strategies will be compared based on all randomized patients, irrespective of whether the patient received all or some of the components of the randomized treatment. Intercurrent events preventing the compliance with these strategies such as initiation of alternative cancer therapies prior to the composite event of interest, will be handled accordingly. A Cox regression model stratified by randomization stratification factors will be used to estimate the hazard ratio (HR) of EFS.

12.4.1 Definition of primary endpoint(s)

The primary endpoint of the study is event-free survival (EFS), defined as the time from the date of randomization to the date of the first documented disease progression or stable disease at or after the week 12 assessment, as assessed by BIRC per Lugano criteria (see [Section 16.2 Appendix 2](#) for further details), or death due to any cause, at any time. The week 12 assessment has a one week visit window, therefore the assessment can occur as early as week 11. Given this visit window, all responses of SD or PD after week 11 will be counted as an event. Censoring conventions are provided in [Section 12.4.3](#).

12.4.2 Statistical model, hypothesis, and method of analysis

The primary efficacy objective is considered to be met if the null hypothesis, i.e. the survival functions for EFS in the two arms are identical, can be rejected based on a one-sided stratified weighted log-rank test at 2.5% level of significance. The weights will be specified in the study statistical analysis plan (SAP). The stratification will be based on the randomization stratification factors, i.e., remission duration (refractory to front line therapy or < 6 months vs. $6 - 12$ months) and IPI score (< 2 vs. ≥ 2).

The analysis of EFS will be based on the FAS according to the randomized treatment arm and strata assigned at randomization. The distribution of EFS will be estimated using the Kaplan-Meier method. Kaplan-Meier curves, medians and 95% confidence intervals of the medians will be presented for each treatment arm. The weighted average log hazard ratio for EFS will be calculated, along with its 95% confidence interval.

There will be no interim analysis for EFS. The analysis for EFS in FAS will be performed after approximately 200 EFS events have been documented by the BIRC. It is estimated that the 200th EFS event will be observed at approximately 23 months from the date of first patient randomized.

12.4.3 Handling of missing values/censoring/discontinuations

If no EFS event is observed prior to the earliest censoring event, EFS will be censored at the date of the last adequate assessment prior to the earliest censoring event. The censoring events include lost to follow-up, withdrew consent, analysis cut-off, missing tumor assessment and initiation of new cancer therapy.

The following scenarios after randomization will be considered as initiation of new cancer therapy and EFS will be censored:

In tisagenlecleucel arm,

- start any anti-CD19 or gene therapy other than tisagenlecleucel,

- start conditional therapy with intention of HSCT
- start any anti-neoplastic therapy at any time after tisagenlecleucel infusion
- start any anti-neoplastic therapy other than protocol allowed optional bridging therapy prior to tisagenlecleucel infusion (this includes patients who had never received tisagenlecleucel infusion)

In the SOC arm,

- start anti-CD19 or gene therapy including tisagenlecleucel
- start any anti-neoplastic therapy other than protocol allowed SOC treatment options

If an EFS event is observed after two or more missing or non-adequate tumor assessments, then EFS will be censored at the last adequate assessment before the EFS event.

12.4.4 Sensitivity and supportive analyses

Due to 4 week delay of CTL infusion, weighted log rank test using the Fleming-Harrington (FH) family of weights, e.g., FH (0, 1) to assign more weight to later events may be used as a sensitivity analysis.

The hazard ratio and 95% confidence interval for EFS per BIRC assessment based on:

- An unstratified and covariate unadjusted Cox model.
- A stratified and covariate adjusted Cox model including as covariates the following: (age, race, gender, geographic region etc.)

EFS as per investigator assessment will be analyzed using a stratified Cox model, with the same analysis conventions as the primary efficacy analysis, and the treatment effect will be summarized by weighted average log hazard ratio with its 95% confidence interval. Kaplan-Meier curves, medians and 95% confidence intervals of the medians will be presented for each treatment group.

EFS analysis considering new anti-cancer therapy for lymphoma at any time as an EFS event

Depending on the amount of missing assessments, further sensitivity analyses maybe considered.

These analyses will include Kaplan-Meier medians with their 95% confidence intervals, and summarized by weighted average log hazard ratio with its 95% confidence interval.

EFS per BIRC review will be analyzed based on the Per Protocol Set, using the same analysis conventions as in the primary efficacy analysis (with the exception of the log-rank test, which will not be performed).

If the primary analysis is statistically significant, subgroup analyses to assess the homogeneity of the treatment effect across demographic and baseline disease characteristics will be performed based on the following:

- Region
- Age: <65 years, \geq 65 years
- Gender: Male, Female
- Race: Asian, Black, Caucasian, Other,

- Ethnicity: Hispanic or Latino, Chinese, Indian, Japanese, Mixed ethnicity, Other
- Prior response status: Primary refractory, relapse
- Histology: DLBCL, NOS, FL3B, Other
- Disease stage at study entry: I/II vs III/IV
- DLBCL cell of origin subtype: GCB, ABC, Other
- Rearrangements in MYC/BCL2/BCL6 genes: Double/Triple hits, Other

In addition, subgroup analyses will be performed on each level of the randomization stratification factors. The analyses will include Kaplan-Meier summaries and hazard ratios (together with associated 95% CI) from stratified Cox models. Subgroup analyses will only be performed if adequate number of events are observed.

The number of subjects censored and reasons for censoring will be summarized by treatment group using descriptive statistics, presented separately for local review and BIRC.

12.5 Analysis of secondary endpoints

The secondary objectives in this study are to compare the two treatment groups with respect to overall survival (OS), and to evaluate the overall response rate (ORR), duration of response (DOR) by BIRC and investigator, PRO, and safety.

There are no key secondary endpoints in this study.

Overall survival (OS), defined as time from the date of randomization to date of death due to any cause, will also be compared between the two treatment arms in FAS, if the primary endpoint (EFS by BIRC) is significant.

Testing of null hypothesis, the survival functions for OS in the two arms are identical, will be conducted by a weighted stratified log-rank test. OS analyses will be made as part a group sequential design using a Hayittle-Peto boundary with 0.0005 at interim. The stratification will be based on the randomization stratification factors, i.e., remission duration refractory to front line therapy or relapsed <6 months vs. relapsed 6 - 12 months), and IPI score (<2 vs. ≥ 2).

Patients in SOC arm are eligible to cross over to tisagenlecleucel treatment, after documented progression of disease or continuation of stable disease at or after the week 12 (± 1 w) assessment, is confirmed by BIRC. The primary analysis of OS will be based on intent-to-treat (ITT) population, i.e., patients randomized to SOC arm who cross over to tisagenlecleucel arm will be considered to be in the SOC arm for OS analysis. As a sensitivity analysis, OS will be censored at time of crossover. In addition, analysis of OS accounting for crossover (for example, rank preserving structural failure model) will be considered.

If death has not been observed by the date of analysis cutoff, OS will be censored at the date of last contact.

Distribution of OS will be estimated using the Kaplan-Meier method. The median OS and the proportion of patients alive at 6, 12 weeks, 6, 12, 18, 24, 36, 48 and 60 months with 95% confidence intervals will be presented by treatment arms. The weighted average log hazard ratio (HR) of OS will be summarized along with 95% confidence interval.

12.5.1 Efficacy and/or pharmacodynamic endpoint(s)

BIRC assessment as well as investigator assessment will be used for the analysis of secondary endpoints that involve disease response. Specifications below are described for BIRC, and the same analyses will be repeated for investigator, unless specified otherwise.

12.5.1.1 Overall response rate (ORR)

Overall response rate (ORR) is defined as the proportion of subjects with best overall response (BOR) of complete response (CR) or partial response (PR), as per BIRC assessment and according to Lugano criteria (see [Section 16.2](#) Appendix 2 for details).

ORR and its 95% confidence interval will be presented by treatment arm. As a sensitivity analysis, ORR as per investigator assessment will be presented by treatment group, along with 95% confidence intervals.

12.5.1.2 Duration of overall response (DOR)

Duration of response (DOR) only applies to patients whose best overall response is complete response (CR) or partial response (PR) according to Lugano criteria based on disease response data per BIRC. It is defined as the time from the date of first documented response of CR or PR to the date of first documented progression (SD or PD at or after the week 12 ($\pm 1w$) assessment will be considered progression) or death due to aggressive B-cell NHL.

In case a patient does not have progression or death due to aggressive B-cell NHL B prior to data cutoff, DOR will be censored at the date of the last adequate assessment on or prior to the earliest censoring event. The same censoring reasons and censoring date options used in the primary EFS analysis will be for DOR.

Distribution of DOR will also be estimated using the Kaplan-Meier method in which death due to reason other than aggressive B-cell NHL will be censored.

DOR will be listed and summarized by treatment group for all subjects in the FAS with patients having BOR of CR or PR.

12.5.2 Safety endpoints

For all safety analyses, the safety set will be used, unless otherwise specified. All listings and tables will be presented by treatment arms.

The overall observation period will be divided into three mutually exclusive segments:

1. Pre-treatment period: from randomization to the first dose of any component of study treatment.
2. On-treatment period: from day of first dose of any component of study treatment to the earlier of:
 - 8 weeks after last dose of study treatment
 - Start date of new cancer therapy other than assigned treatment
3. Post-treatment period: after end of on-treatment period:

Primary safety summaries (tables, figures) by treatment arms include only data from the on-treatment period with the exception of baseline data which will also be summarized where

appropriate (e.g. change from baseline summaries). All safety data will be summarized and listed by treatment period.

In addition, safety data after tisagenlecleucel infusion will be separately summarized (including patients received tisagenlecleucel infusion in either arm A or patients crossed-over from arm B).

Adverse events

All information obtained on adverse events will be displayed by treatment arm and patient.

The number (and percentage) of patients with treatment emergent adverse events will be summarized in the following ways:

- by treatment, primary system organ class and preferred term.
- by treatment, primary system organ class, preferred term and maximum severity.

Summary tables for adverse events will be provided for AEs that started or worsened during the post-randomization period. All safety data will be listed by reporting period.

The incidence of adverse events during the on-treatment period will be summarized by primary system organ class (SOC), preferred term, severity (based on CTCAE grades), and relation to study treatment by treatment arm. The frequency of Common Toxicity Criteria (CTC) grade 3 and 4 AEs will be summarized separately.

Separate summaries will be provided for study medication related adverse events, death, serious adverse events, other significant adverse events leading to discontinuation.

The number (and proportion) of patients with adverse events of special interest (AESI) will be summarized by treatment. The current search criteria of AESI are based on limited experience from ongoing clinical studies without an accurate assessment of causality. AESI and the search criteria of AESI will be updated prior to reporting. AESI that occur within 8 weeks of the tisagenlecleucel infusion will be summarized by group term and preferred term.

A patient with multiple adverse events within a primary system organ class is only counted once towards the total of the primary system organ class.

Adverse events which will be counted for a specific treatment period are those which are treatment-emergent. These events are those with an onset after the start of the treatment period, or which were present prior to the start of the treatment period but increased in severity, changed from being not suspected to being suspected of study drug relationship, or developed into SAEs after the start of the treatment period.

Summary tables for adverse events (AEs) will include only AEs that started or worsened during the on-treatment period, the **treatment-emergent** AEs.

The incidence of treatment-emergent adverse events (new or worsening from baseline) will be summarized by system organ class and or preferred term, severity (based on CTCAE grades), type of adverse event, relation to study treatment.

Serious adverse events, non-serious adverse events and adverse events of special interest (AESI) during the on-treatment period will be tabulated.

All AEs, deaths and serious adverse events (including those from the pre and post-treatment periods) will be summarized and listed and those collected during the pre-treatment and post-treatment period will be flagged.

Vital signs

All vital signs data will be listed by treatment group, patient, and visit and if ranges are available, abnormalities will be flagged. Summary statistics will be provided by treatment.

12-lead ECG

12-lead ECGs including PR, QRS, QT, QTcF intervals and heart rate (HR) will be obtained for each patient during the study. ECG data will be read and interpreted (centrally/locally).

Categorical Analysis of QT/QTc interval data based on the number of patients meeting or exceeding predefined limits in terms of absolute QT/QTc intervals or changes from baseline will be presented. In addition, a listing of these patients will be produced by treatment arm.

All ECG data will be listed by treatment arm, subject and visit, abnormalities will be flagged. Summary statistics will be provided by treatment and visit.

Clinical laboratory evaluations

Grading of laboratory values will be assigned programmatically as per NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5. The calculation of CTCAE grades will be based on the observed laboratory values only, clinical assessments will not be taken into account.

CTCAE Grade 0 will be assigned for all non-missing values not graded as 1 or higher. Grade 5 will not be used.

For laboratory tests where grades are not defined by CTCAE v5, results will be categorized as low/normal/high based on laboratory normal ranges.

The following summaries will be generated separately for hematology, and biochemistry tests by treatment arm:

For laboratory tests where grades are defined by CTCAE v5

- Worst post-baseline CTCAE grade (regardless of the baseline status). Each patient will be counted only once for the worst grade observed post-baseline.
- Shift tables using CTCAE v5 grades to compare baseline to the worst on-treatment value for SOC and to compare baseline to the worst post-infusion value for CTL arm

For laboratory tests where grades are not defined by CTCAE v5,

- Shift tables using the low/normal/high/ (low and high) classification to compare baseline to the worst on-treatment value.

Listing of all laboratory data with values flagged to show the corresponding CTCAE v5 grades if applicable and the classifications relative to the laboratory normal ranges.

In addition to the above mentioned tables and listings, other exploratory analyses, for example figures plotting time course of raw or change in laboratory tests over time or box plots might be specified in the Statistical Analysis Plan (SAP).

Other safety evaluations

Presence of detectable RCL will be tested by VSV-G at scheduled assessments. All safety data will be listed.

Safety subgroup analysis

Key safety summaries for adverse events regardless of relationship to study drug by System, Organ, Class (SOC) and PT, and adverse events of special interest will be repeated on the Safety Set in the following subgroups of age, gender, race, ethnicity, histology, and DLBCL cell of origin subtype subgroups.

Summary tables will only be performed if at least 5 patients are present in each subgroup. Some grouping of classes will be considered.

Immunogenicity

The humoral immunogenicity assay measures the antibody titers specific to the tisagenlecleucel molecule prior to and following infusion. Data will be further fractionated to determine proportion of subjects who make transient versus sustained antibody responses. The cellular immunogenicity assay assesses the presence of T lymphocytes activated by the tisagenlecleucel protein. Data will be reported as summary statistics of pre and post-dose levels of activated T lymphocytes. Cellular kinetic parameters, efficacy and concentration time profiles will be summarized according to pre-existing and treatment-induced immunogenicity categories in Arm A and patients who have crossed over to tisagenlecleucel.

Resource utilization

Data relating to resource utilization will be used for the purpose of economic evaluation and will be carried out and reported as a separate activity.

Hospitalizations will be evaluated in this study as an exploratory endpoint to characterize the impact of study treatment on this aspect of healthcare resource utilization. In addition, these data may be used to support assessments used to characterize the economic impact of study treatment regimens. Hospitalization data of interest will focus on those hospitalizations reported within the first 6 months after randomization.

Hospitalizations as a result of the following reasons are not to be reported:

- Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
- Social reasons and respite care in the absence of any deterioration in the subject's general condition
- Treatments occurring on an emergency outpatient basis that does not result in hospital admission and involves an event not fulfilling any of the definitions of a SAE as described in [Section 10.1.2](#) are not required.

Healthcare resource utilization data regarding hospitalizations should be captured from randomization (Day 1) up to Month 6 for the subject as described in [Table 8-2](#) and [Table 8-3](#).

12.5.3 Patient reported outcomes

PRO data from FACT-Lym, EQ-5D-5L and the SF-36 v2 (Acute form) will be assessed during the study as indicated in [Table 8-1](#), [Table 8-2](#), [Table 8-3](#), and [Table 8-4](#). Summary scores will be generated by summing the item responses on the questions for each domain in accordance with the respective scoring manual provided by the developers. Descriptive statistics (e.g. mean, median and frequency) and change from baseline of the summary scores for each post baseline time-point/window of assessment will be provided by treatment arm (tisagenlecleucel and SOC) and cross-over, respectively. FAS will be used for all analysis.

For each treatment group and at each time point, the number and percentage of patients who complete the SF-36 v2, FACT-Lym, and EQ5D will be summarized in a table.

12.5.3.1 SF-36 v2

The SF-36 comprises 36 questions, which can be summarized in eight health domain scores and further combined into a physical component summary (PCS) and a mental component summary (MCS) score. Domain and component summary scores will be converted to norm-based scores based on the general population. A higher SF-36 score denotes better quality of life.

Summary statistics will be reported for each of domains and components over time by treatment arm. Repeated measures mixed-effects model will be carried to compare the two groups with respect to the change from baseline.

Time to definitive deterioration for PCS and MCS will be summarized using Kaplan-Meier methods. Time to definitive deterioration is defined as the time from randomization to the earliest time when the patient's score shows at least 3 points or higher decrease from baseline (with no later change below this threshold). Time to definitive deterioration in each of the eight health domain will also be analyzed. The log-rank test will be used to compare the time to definitive deterioration between the two treatment groups. Rates of improvement for PCS and MCS will be evaluated from baseline to each time point and will be compared between the two treatment groups using chi-square test. Improvement is defined as increase of at least 3 points for PCS and MCS ([Swigris et al 2010](#); [Oerlemans et al 2011](#); [Mehta et al 2017](#)).

12.5.3.2 FACT-Lym

Functional Assessment of Cancer Therapy-Lymphoma (FACT-Lym) is an extension of the FACT-General (FACT-G) standardized assessment of patients that includes the lymphoma subscale (FACT-LymS). The FACT-G is divided into 4 domains: physical, social/family, emotional, and functional well-being. The FACT-LymS is an additional 15 questions meant to evaluate response to treatment and symptoms associated with lymphoma. The FACT-Lym also includes the trial outcome index (FACT-Lym TOI) and the total score (FACT-Lym TS).

Summary statistics will be reported for each of scales over time by treatment arm. Repeated measures mixed-effects model will be carried to compare the two groups with respect to the

change from baseline for FACT-G total score, FACT-LymS, FACT-Lym TOI and FACT-Lym TS.

Time to definitive deterioration for FACT-G total score (≥ 3 decrease), FACT-LymS (≥ 2.9 decrease), FACT-Lym TOI (≥ 5.5 decrease) and FACT-Lym TS (≥ 6.5 decrease) will be summarized using Kaplan-Meier methods. Time to definitive deterioration is defined as the time from randomization to the earliest time when the patient's score shows the above decrease from baseline (with no later change below this threshold). The log-rank test will be used to compare the time to first deterioration between the two treatment groups.

Rates of improvement for these four scores will be evaluated from baseline to each time point and will be compared between the two treatment groups using chi-square test. Improvement is defined as increase of at least 3 points, 2.9 points, 5.5 points, and 6.5 points for FACT-G total score, FACT-LymS, FACT-Lym TOI, and FACT-Lym TS respectively ([Webster et al 2003](#); [Carter et al 2008](#)).

12.5.3.3 EQ-5D-5L

The EQ-5D-5L questionnaire consists of the EQ-5D descriptive system and a visual analogue scale (the EQ-VAS). The EQ-5D descriptive system measures a patient's health state on 5 dimensions which include: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The respondent's self-rated health is assessed on a scale from 0 (worst imaginable health state) to 100 (best imaginable health state) by the EQ-VAS.

Summary statistics will be reported for EQ-VAS over time by treatment arm. Repeated measures mixed-effects model will be carried to compare the two groups with respect to the change from baseline.

Time to definitive deterioration for EQ-VAS is defined as the time from randomization to the earliest time when the patient's score shows at least 7 points or higher decrease from baseline (with no later change below this threshold). The log-rank test will be used to compare the time to first deterioration between the two treatment groups.

Rates of improvement for EQ-VAS will be evaluated from baseline to each time point and will be compared between the two treatment groups using chi-square test. Improvement is defined as increase of at least 7 points ([Kantarjian et al 2016](#)).

For the EQ-5D health state profiles, the proportions of patients reported having "no", "slight", "moderate", "severe", or "extreme" problems at each time point will be reported for each of the 5 dimensions.

12.5.4 Cellular kinetics

Tisagenlecleucel concentrations in peripheral blood (and bone marrow and CSF if available) will be listed, graphed and summarized (arithmetic and geometric means, standard deviation, CV%, CV% geometric mean, minimum, median and maximum) by time points and Month 3 response as assessed by the following:

- Tisagenlecleucel transgene levels as measured by q-PCR
- Tisagenlecleucel transduced cells measured by flow cytometry of CD3-positive/ CD4-positive and CD3-positive/CD8-positive tisagenlecleucel transduced cells if feasible.

The cellular kinetics parameters listed in [Table 8-9](#) along with other relevant cellular kinetics parameters will be estimated, if feasible, from the individual concentration versus time profiles using a non-compartmental approach within the modeling program Phoenix[®] (Pharsight, Mountain View, CA) and reported by best response category. The non-quantifiable concentrations will be imputed to zero for PK concentration summaries, and will not be included for estimation of cellular kinetics parameters. Results reported but deemed unreliable will be flagged and excluded from the summaries and cellular kinetics parameter derivations.

Descriptive statistics of cellular kinetics parameters (arithmetic and geometric means, standard deviation, CV%, CV% geometric mean, minimum, median and maximum) will be summarized by Month 3 response for Arm A as well as for patients who crossover and receive tisagenlecleucel. For T_{max} and T_{last} only minimum, median and maximum will be presented.

For patients whose tocilizumab PK data were collected during CRS, the tocilizumab concentrations will be summarized by time points, relative to time of tocilizumab dose. Tocilizumab concentrations and relevant PK parameters will be summarized by CRS grade for the TPAS for Arm A and patients who crossover and receive tisagenlecleucel.

The relationship between tisagenlecleucel cellular kinetics and dose and response will be explored using appropriate logistic regression and cox regression models if sufficient data is available for Arm A and for patients who crossover and receive tisagenlecleucel. Further details will be provided in the SAP.

12.5.5 Biomarkers

As a project standard, Novartis Oncology Biostatistics and Data Management will analyze only biomarkers collected in the clinical database. Studies are often not adequately powered to assess specific biomarker-related hypotheses, for this reason the exploratory biomarker analyses should be considered as promoting the generation of new scientific hypotheses or observing new trends. These hypotheses may be compared with results found in literature as well as verified with data derived from subsequent clinical trials. No adjustment for multiple comparisons is usually planned for exploratory analyses. Additional post hoc exploratory assessments are expected and may be performed.

Additional analysis may be performed after the completion of the end-of-study CSR and will be documented in separate reports. These analyses may include but are not limited to the meta-analysis of data from this study combined with data from other studies or the analysis of biomarkers generated from samples collected during the study but analyzed after the database lock and completion of the CSR. The data analysis will be described in an addendum of the SAP or in a stand-alone analysis plan document, as appropriate.

There may be circumstances when a decision is made to stop sample collection, or not perform or discontinue the analysis due to either practical or strategic reasons (e.g. issues related to the quality and/or quantity of the sample or issues related to the assay). Under such circumstances, the number of samples may be inadequate to perform a rigorous data analysis and the available data will only be listed and potentially summarized.

12.5.5.1 Biomarker data analysis set

The Full Analysis Set will be used for all biomarker analysis. Unless otherwise specified, all statistical analyses of biomarker data will be performed on patients with biomarker data.

12.5.5.2 Data handling

Serum cytokine values below the lower limit of quantitation (which may be reported with the label Lower Limit of Quantification [LLOQ]) or have a numerical value below the assay's lower limit of quantification) will be imputed / replaced as $0.5 \times \text{LLOQ}$, which will be specified by the performing lab and is assay and analyte specific. In some cases a value, although below LLOQ, is reported, this value should not be used and the data should be imputed as $0.5 \times \text{LLOQ}$.

12.5.5.3 PD-1, PD-L1 and PD-L2 status and other exhaustion markers

CD19 expression in tumor biopsy specimens at baseline, PD-1 and PD-L1 expression levels and their interaction score if available will be listed and summarized for Arm A and crossover patients. CD19, PD-1, PD-L1 and PD-1/PD-L1 interaction score will also be summarized by clinical response for Arm A and progressive disease patients.

12.5.5.4 Soluble immune factors

The profile of blood soluble proteins and inflammatory cytokines and receptors (IL-10, interferon gamma, IL-6, CRP, and ferritin) will be listed and summarized by patient and time point for Arm A and crossover patients. Baseline and absolute and relative change (percent and or fold change) from baseline will be calculated for each time point and summarized using sample size, mean, standard deviation, median, minimum and maximum. If both the baseline and post baseline values are below Lower Limit of Quantification (LLOQ), absolute, percent and fold change from baseline will not be imputed and reported as missing. Baseline levels may also be summarized by clinical response status and relevant adverse events and potentially graphed using strip plots. In addition, the maximum change from baseline measure for each cytokine may also be graphed against clinical response status and relevant adverse events using strip plots. Patient level and averaged cytokine measures and percent change from baseline may be displayed using longitudinal plots.

12.5.5.5 MRD by Ig deep sequencing

MRD by Ig deep sequencing may be used to identify the dominant tumor clone sequence in blood at baseline and to track clearance or re-appearance of the same clone sequence in subsequent analysis time points. The tumor clonal distribution may be listed for Arm A and cross-over patients and percent change from baseline will be summarized if applicable. Patient level absolute and relative changes may be displayed using longitudinal plots. Association between MRD and clinical outcome may be performed.

12.5.5.6 Genomic and/or Next Generation Sequencing (NGS) analysis

Genomic and/or NGS analysis in relation with clinical endpoints will be performed and documented in separate reports.

Potential analysis exploring relationship of efficacy/safety endpoints with tumor cells mutation and/or gene expression could be also conducted. Analysis of leukocyte transcriptome changes pre and post tisagenlecleucel administration and the correlations between apheresis/cell product and clinical responses (efficacy, safety and PK parameters) will be summarized in a separate report.

12.5.5.7 B cell and T cell characterization

The levels of blood B and/or T cells will be listed and summarized by patient and time point for all enrolled patients. Absolute number and/or frequencies of total B cell populations will be listed and summarized by patient and time point. Baseline and change from baseline to minimum cell number may also be summarized by response status and potentially graphed using strip plots.

T cell subsets by immunophenotyping within tisagenlecleucel positive and/or tisagenlecleucel negative populations will be explored in relation to safety and efficacy endpoints for Arm A and cross-over patients. Data may also be summarized by response status and CRS severity and potentially graphed using strip plots. Patient level and average longitudinal plots of the cell counts and percent changes from baseline may be generated.

12.5.5.8 Molecular characteristics of tisagenlecleucel apheresis product /final product

Apheresis product and/or final product molecular read-outs (e.g. immune cell subsets, T cell differentiation and exhaustion markers, gene expression) will be assessed, listed and summarized by clinical response and/or relevant adverse events for Arm A and cross-over patients and summarized in a separate report.

12.5.6 Correlation of baseline rituximab levels with clinical response

Selected clinical outcomes (ORR, DOR, EFS and OS) will be summarized descriptively by the rituximab levels at baseline.

12.5.7 Efficacy in sub-populations

Clinical outcomes (ORR, DOR, EFS and OS) will be summarized descriptively by the following sub-populations:

- Immunogenicity to tisagenlecleucel:
- prevalence of immunogenicity against tisagenlecleucel (pre-existing), both humoral and cellular
- incidence of immunogenicity against tisagenlecleucel, both humoral and cellular
- Double-hit/triple-hit patients with Bcl-2, Bcl-6 and c-myc expression

12.6 Analysis of exploratory endpoints

12.6.1 Efficacy and safety after cross-over

The main efficacy and safety endpoints (ORR, OS AE and PRO) will also be summarized after tisagenlecleucel infusion for patients crossed over to tisagenlecleucel arm.

12.6.2 Healthcare resource utilization

Data relating to resource utilization will be used to support health economic evaluations.

Number of tisagenlecleucel inpatients and outpatients infusions will be summarized. Descriptive statistics of hospitalizations, including the total and average number and duration of hospitalizations, will be provided by treatment arm.

Details of data analysis will be specified in the analysis plan as appropriate.

12.7 Interim analyses

No interim analysis is planned for this trial for the primary endpoint of EFS. A hierarchical testing procedure will be adopted and the statistical test for OS will be performed only if the primary efficacy endpoint, EFS is statistically significant.

A maximum of two analyses are planned for OS: 1) an interim analysis at the time of the primary analysis for EFS (provided EFS is significant, as outlined in [Section 12.5](#)) in FAS and 2) a final analysis for OS at approximately 5 years from the first patient randomized. Haybittle–Peto boundary will be used for testing OS.

12.8 Sample size calculation

12.8.1 Primary endpoint(s)

Based on the data from the ORCHARRD study (Novartis unpublished analyses), EFS time for patients who were randomized to receive salvage chemotherapy (DHAP plus Rituximab or DHAP plus Ofatumumab), who never reached CR before or relapsed within 12 months from response to previous therapy, or had a response of PR, SD or PD to previous therapy was considered as a reference for SOC. In ORCHARRD study, for these patients, who continue to be in SD status at the end of cycle 2/3 (which is earlier than the 12 week assessment, each cycle: 21 days) or had progressed earlier than the 12 week assessment, based on the definition of EFS endpoint used in BELINDA (where patients with documented SD/PD at the 12 week assessment (+/-1 week) is considered an EFS event), EFS event time was adjusted to 12 weeks, to account for these earlier events.

The 9 month EFS rate is estimated to be 22.32% in SOC arm and is assumed to be 40% in CTL arm. Due to delayed CTL infusion of 6 weeks and ignoring SD/PD at week 6, we assume piecewise hazard rate in both treatment arms. The hazard ratio between two arms during the first 6 weeks is assumed to be 1 and 0.61 after 6 weeks. Given those assumptions, a total of 200 EFS events are required to have 92% power at an one-sided 2.5% level of significance to reject the null hypothesis (i.e. the survival functions for EFS in the two arms are identical), using a stratified log rank test with equal weights. The sample size calculation was conducted via simulation with software package East 6.4.

Considering a recruitment period of approximately 21 months using staggered enrollment rate of 2, 10, 16 patients in the 1st 3 months followed by 17 patients thereafter, and assuming 15% drop out rate, a total of approximately 318 patients will need to be randomized to the two treatment arms in a 1:1 ratio. Given the above assumptions, it is estimated that the 200th EFS event will be observed at approximately 23 months from the date of first patient randomized.

13 Ethical considerations and administrative procedures

13.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented, executed and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US CFR 21), and with the ethical principles laid down in the Declaration of Helsinki.

13.2 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g., advertisements) and any other written information to be provided to subjects. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

13.3 Publication of study protocol and results

The protocol will be registered in a publicly accessible database such as clinicaltrials.gov and as required in EudraCT. In addition, after study completion (defined as last patient last visit) and finalization of the study report the results of this trial will be submitted for publication and posted in a publicly accessible database of clinical trial results, such as the Novartis clinical trial results website and all required Health Authority websites (e.g. Clinicaltrials.gov, EudraCT etc).

For details on the Novartis publication policy including authorship criteria, please refer to the Novartis publication policy training materials that were provided to you at the trial investigator meetings.

13.4 Quality control and quality assurance

Novartis maintains a robust Quality Management System (QMS) that includes all activities involved in quality assurance and quality control, to ensure compliance with written Standard Operating Procedures as well as applicable global/local GCP regulations and ICH Guidelines.

Audits of investigator sites, vendors, and Novartis systems are performed by auditors, independent from those involved in conducting, monitoring or performing quality control of the clinical trial. The clinical audit process uses a knowledge/risk based approach.

Audits are conducted to assess GCP compliance with global and local regulatory requirements, protocols and internal SOPs, and are performed according to written Novartis processes.

14 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of subjects should be administered as deemed necessary on a case by case basis. Under no circumstances including incidental collection is an investigator allowed to collect additional data or conduct any additional procedures for any purpose involving any investigational drugs under the protocol, other than the purpose of the study. If despite this interdiction prohibition, data, information, observation would be incidentally collected, the investigator shall immediately disclose it to Novartis and not use it for any purpose other than the study, except for the appropriate monitoring on study participants.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC and health authorities, where required, it cannot be implemented.

14.1 Protocol Amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, health authorities where required, and the IRB/IEC prior to implementation.

Only amendments that are required for subject safety may be implemented immediately provided the health authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified.

Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any subject included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations.

15 References

A Predictive Model for Aggressive Non-Hodgkin's Lymphoma - The International Non-Hodgkin's Lymphoma Prognostic Factors Project (1993) *N Engl J Med*; 329:987-94.

Al-Hamadani M, Habermann TM, Cerhan JR, et al (2015) Non-Hodgkin lymphoma subtype distribution, geodemographic patterns, and survival in the US: A longitudinal analysis of the National Cancer Data Base from 1998 to 2011. *Am J Hematol*; 90(9):790-5.

Alizadeh AA, Eisen MB, Davis RE, et al (2000) Distinct types of diffuse large B-cell lymphoma identified by gene expression profiling. *Nature*; 403(6769):503-511.

Anon (2006a) Guidance for industry: gene therapy clinical trials-observing subjects for delayed adverse events; availability. Available from <https://www.federalregister.gov/articles/2006/11/28/E6-20129/guidance-for-industry-gene-therapy-clinical-trials-observing-subjects-for-delayed-adverse-events> (Accessed 13 March 2017).

Anon (2006b) Guidance for industry: supplemental guidance on testing for replication competent retrovirus in retroviral vector based gene therapy products and during follow-up of patients in clinical trials using retroviral vectors. Available from <http://www.fda.gov/biologicsbloodvaccines/guidancecomplianceregulatoryinformation/guidances/cellularandgenetherapy/ucm072961.htm>.

Anon (2009) Guideline on follow-up of patients administered with gene therapy medicinal products. Available from http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/11/WC500013424.pdf.

Averbeck M, Gebhardt C, Emmrich F, et al (2007) Immunologic principles of allergic disease. *J Dtsch Dermatol Ges*; 5(11):1015-28.

Awasthi R, Tam CS, Jaeger U, et al (2017) Clinical Pharmacology of CTL019 in Patients with Relapsed/Refractory (r/r) Diffuse Large B-Cell Lymphoma (DLBCL). *Blood*; 130:5211.

Baetz T, Belch A, Couban S, et al (2003) Gemcitabine, dexamethasone and cisplatin is an active and non-toxic chemotherapy regimen in relapsed or refractory Hodgkin's disease: a phase II study by the National Cancer Institute of Canada Clinical Trials Group. *Ann Oncol*; 14:1762-1767.

Barrington SF, Mikhaeel NG, Kostakoglu L, et al (2014) Role of imaging in the staging and response assessment of lymphoma: consensus of the international conference on malignant lymphomas imaging working group. *J Clin Oncol*; 32:3048-58.

Bendamustine full prescribing information. Available from: dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=39d53698-57fa-7c99-fc5b-f52a55684826#section-5.6. Accessed 13Mar2017.

Bonifant CL, Jackson HJ, Brentjens RJ, et al (2016) Toxicity and management in CAR T-cell therapy. *Mol Ther Oncolytics*; 3:16011. doi: 10.1038/mto.2016.11. eCollection 2016.

Botzug K, Schmidt M, Schwarzer A, et al (2010) Stem-cell gene therapy for the Wiskott-Aldrich syndrome. *N Engl J Med*; 363(20):1918-1927.

- Brentjens R, LaTouche JB, Santos E, et al (2003) Eradication of systemic B-cell tumors by genetically targeted human T lymphocytes co-stimulated by CD80 and interleukin-15. *Nat Med*; 9:279-286.
- Brentjens R, Riviere I, Park JH, et al (2011) Safety and persistence of adoptively transferred autologous CD19-targeted T cells in patients with relapsed or chemotherapy refractory B-cell leukemias. *Blood*; 118(18):4817-28.
- Brentjens R, Yeh R, Bernal Y, et al (2010) Treatment of chronic lymphocytic leukemia with genetically targeted autologous T cells: case report of an unforeseen adverse event in a phase I clinical trial. *Mol Ther*; 18(4):666-668.
- Cairo MS, Bishop M (2004) Tumor lysis syndrome: new therapeutic strategies and classification. *Br J Haematol*; 127(1): 3-11.
- Calogero A, DeLeij LF, Mulder NH, et al (2000) Recombinant T-cell receptors: an immunologic link to cancer therapy. *J Immunol*; 23(4):393-400.
- Carter GC, Liepa AM, Zimmermann AH, et al (2008) Validation of the Functional Assessment of Cancer Therapy–Lymphoma (FACT-LYM) in Patients with Relapsed/Refractory Mantle Cell Lymphoma. *Blood*; 112:2376.
- Chavey WE, Blaum CS, Bleske BE, et al (2001) Guideline for the management of heart failure caused by systolic dysfunction: Part I. Guideline development, etiology and diagnosis. *Am Fam Physician*; 64(5):769-74.
- Cheson BD, Fisher RI, Barrington SF, et al (2014) Recommendations for initial evaluation, staging, and response assessment of Hodgkin and Non-Hodgkin lymphoma: The Lugano Classification. *J Clin Oncol*; 32:3059-3067.
- Cheson BD, Horning SJ, Coiffier B, et al (1999) Report of an international workshop to standardize response criteria for non-Hodgkin's lymphomas. *J Clin Oncol* 17:1244-1253.
- Cheson BD, Pfistner B, Juweid ME, et al (2007) Revised response criteria for malignant lymphoma. *J Clin Oncol* 25:579-586.
- FDA Guideline (2007) Clinical trial endpoints for the approval of cancer drugs and biologics, May 2007.
- Chiappella A, Castellino A, and Vitolo U (2016) State-of-the-art Therapy for Advanced-stage Diffuse Large B-cell Lymphoma. *Hematol Oncol Clin North Am*; 30(6): 1147–1162.
- Clay TM, Morse M, Lyster HK (2002) Redirecting cytotoxic T lymphocyte responses with T-cell receptor transgenes. *Expert Opin Biol Ther*; 2(4):353-360.
- Coiffier B, Sarkozy C (2016) Diffuse large B-cell lymphoma: R-CHOP failure-what to do? *Hematology Am Soc Hematol Educ Program*; (1):366-378.
- Corominas M, Gastaminza G, Lobera T (2014) Hypersensitivity reactions to biological drugs. *J Investig Allergol Clin Immunol*; 24(4):212-25.
- Cramer SP, Modvig S, Simonsen HJ, et al (2015) Permeability of the blood–brain barrier predicts conversion from optic neuritis to multiple sclerosis. *Brain*; 138:2571–2583.
- Crump M, Kuruvilla J, Couban S, et al (2014) Randomized Comparison of Gemcitabine, Dexamethasone and Cisplatin Versus Dexamethasone, Cytarabine, and Cisplatin

Chemotherapy Before Autologous Stem-Cell Transplantation for Relapsed and Refractory Aggressive Lymphomas: NCIC-CTG LY.12. *J Clin Oncol*; 32(31):3490-3496.

Crump M, Neelapu SS, Farooq U, et al (2017) Outcomes in refractory aggressive diffuse large b-cell lymphoma (DLBCL): Results from the international SCHOLAR-1 study. *Blood*;130(16):1800-1808.

Cyclophosphamide full prescribing information. Available from: dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=591d9955-3d9c-4cdc-a308-2f1288376b9f. Accessed 13Mar2017.

Descotes J (2012) Safety immunopharmacology: evaluation of the adverse potential of pharmaceuticals on the immune system. *J Pharmacol Toxicol Methods*; 66(2):79-83.

Dreyling M, Ghielmini M, Rule S, et al (2016) Newly Diagnosed and Relapsed Follicular Lymphoma: ESMO Clinical Practice Guidelines Diagnosis, Treatment, and Follow-up. *Ann Oncol*; 27Suppl 5: 83-90.

Dudley M, Wunderlich J, Robbins P, et al (2002) Cancer regression and autoimmunity in patients after clonal repopulation with antitumor lymphocytes. *Science*; 298:850-854.

Dudley M, Wunderlich J, Yang J, et al (2005) Adoptive cell transfer therapy following nonmyeloablative but lymphodepleting chemotherapy for the treatment of patients with refractory metastatic melanoma. *J Clin Oncol*; 23(10):2346-57.

Dummer W, Niethammer AG, Baccala R, et al (2002) T cell homeostatic proliferation elicits effective antitumor autoimmunity. *J Clin Invest*; 110(2):185-192.

Elstrom RL, Martin P, Ostrow K, et al (2010) Response to second-line therapy defines the potential for cure in patients with recurrent diffuse large B-cell lymphoma: implications for the development of novel therapeutic strategies. *Clin Lymphoma Myeloma Leuk*; 10(3):192-196.

Eshhar Z, Waks T, Bendavid A, et al (2001) Functional expression of chimeric receptor genes in human T cells. *J Immunol Methods*; 248:67-76.

Feldman A, Gurevich M, Huna-Baron, et al (2015) The Role of B Cells in the Early Onset of the First Demyelinating Event of Acute Optic Neuritis. *IOVS*; 56(2):1349-1356.

Ferlay J, Soerjomataram I, Dikshit R, et al (2015) Cancer Incidence and Mortality Worldwide: Sources, methods, and major patterns in GLOBOCAN 2012. *Int J Cancer*; 136:E359-E386.

Finney HM, Akbar AM, Lawson AD (2004) Activation of resting human primary T cells with chimeric receptors: costimulation from CD28, inducible, costimulator, CD134 and CD137 in series with signals from the TCR zeta chain. *J Immunol*; 172:104-113.

Finney HM, Lawson AD, Bebbington CR, et al (1998) Chimeric receptors providing both primary and costimulatory signaling in T cells from a single gene product. *J Immunol*; 161:2791-2797.

Fitzgerald J, Weiss S, Maude S, et al (2017) Cytokine Release Syndrome After Chimeric Antigen Receptor T Cell Therapy for Acute Lymphoblastic Leukemia. *Crit Care Med*; 45(2):e124-e13.

Fludarabine full prescribing information. Available from:

dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=fb70b8e8-aca8-4d67-8791-063ac4081073. Accessed 13Mar2017.

Friedberg JW (2011) Relapsed/refractory diffuse large B-cell lymphoma. Hematology Am Soc Hematol Educ Program; 2011:498-505.

Friedmann-Morvinski D, Bendavid A, Waks T, et al (2005) Redirected primary T cells harboring a chimeric receptor require costimulation for their antigen-specific activation. Blood; 105:3087-3093.

Gisselbrecht C, Glass B, Mounier N, et al (2010) Salvage regimens with autologous transplantation for relapsed large B-cell lymphoma in the rituximab era. J Clin Oncol; 28(27): 4184-4190.

Goldrath AW, Bevan MJ (1999) Selecting and maintaining a diverse T-cell repertoire. Nature; 402(6759):255-262.

Gopal AK, Kahl BS, de Vos S, et al (2014) PI3K δ inhibition by idelalisib in patients with relapsed indolent lymphoma. N Engl J Med; 370(11):1008-18.

Gross G, Eshhar Z (1992) Endowing T cells with antibody specificity using chimeric T cell receptors. FASEB J; 6:3370-3378.

Gross G, Waks T, Eshhar Z (1989) Expression of immunoglobulin-T-cell receptor chimeric molecules as functional receptors with antibody-type specificity. Proc Natl Acad Sci USA; 86(24):10024-10028.

Grupp SA, Kalos M, Barrett D, et al (2013) Chimeric antigen receptor-modified T cells for acute lymphoid leukemia. N Engl J Med; 368(16):1509-1518.

Hacein-Bey-Abina S, vonKalle C, Schmidt M, et al (2003) LMO2-associated clonal T cell proliferation in two patients after gene therapy for SCID-X1. Science; 302:415-419.

Hans CP, Weisenburger DD, Greiner TC, et al (2004) Confirmation of the molecular classification of diffuse large B-cell lymphoma by immunohistochemistry using a tissue microarray. Blood; 103(1):275-282.

Hedger MP, Meinhardt A (2000) Local regulation of T cell numbers and lymphocyte inhibiting activity in the interstitial tissue of the adult rat testis. J Reprod Immunol; 48(2): 69–80Kewalramani 2004.

Hombach A, Heuser C, Abken H (2002) The recombinant T cell receptor strategy: insights into structure and function of recombinant immunoreceptors on the way towards an optimal receptor design for cellular immunotherapy. Curr Gene Ther; 2:211-226.

Howe SJ, Mansour MR, Schwarzwaelder K, et al (2008) Insertional mutagenesis combined with acquired somatic mutations causes leukemogenesis following gene therapy of SCID-X1 patients. J Clin Invest; 118(9):3143-3150.

Howlader N, Noone A, Krapcho M (2011) SEER Cancer Statistics Review (CSR) 1975-2015. Available from: http://seer.cancer.gov/csr/1975_2011, Accessed on 14/May/2017.

Jaffe ES (2009) 2008 WHO classification of lymphomas: implications for clinical practice and translational research. Hematology Am Soc Hematol Educ Program :523-31.

- June CH, Blazar BR, Riley JL (2009) Engineering lymphocyte subsets: tools, trials and tribulations. *Nat Rev Immunol*; 9:704-716.
- June CH (2007) Adoptive T cell therapy for cancer in the clinic. *J Clin Invest*; 117(6):1466-1476.
- Kaech SM, Ahmed R (2001) Memory CD8⁺ T cell differentiation: Initial antigen encounter triggers a developmental program in naïve cells. *Nat Immunol*; 2(5):415-422.
- Kamel H, Iadecola C (2012) Brain-Immune Interactions and Ischemic Stroke. *Arch Neurol*; 69(5):576-581.
- Kantarjian HM, Su Y, Jabbour EJ, et al (2016) Patient-Reported Outcomes From a Global Phase 3 Randomized Controlled Trial of Inotuzumab Ozogamicin Versus Standard of Care Chemotherapy for Relapsed/Refractory Acute Lymphoblastic Leukemia. Presented at American Society of Hematology 58th Annual Meeting and Exposition; December 3–6, 2016, San Diego, CA, USA.
- King C, Ilic A, Koelsch K, et al (2004) Homeostatic Expansion of T Cells during Immune Insufficiency Generates Autoimmunity. *Cell*; 117(2):265-277.
- Klebanoff CA, Khong HT, Antony PA, et al (2005) Sinks, suppressors and antigen presenters: how lymphodepletion enhances T cell-mediated tumor immunotherapy. *Trends Immunol*; 26(2):111-117.
- Kohn DB, Dotti G, Brentjens R (2011) CARs on track in the clinic. *Mol Ther*; 19(3):432-38.
- Krause A, Guo HF, Latouche JB, et al (1998) Antigen-dependent CD28 signaling selectively enhances survival and proliferation in genetically modified activated human primary T lymphocytes. *J Exp Med*; 188(4):619-626.
- Lamers CH, Langeveld SC, Groot-van Ruijven CM, et al (2007) Gene-modified T cells for adoptive immunotherapy of renal cell cancer maintain transgene-specific immune functions in vivo. *Cancer Immunol Immunother*; 56(12):1875-1883.
- Lamers CHJ, Sleijfer S, Vulto AG, et al (2006) Treatment of metastatic renal cell carcinoma with autologous T-lymphocytes genetically retargeted against carbonic anhydrase ix: first clinical experience. *J Clin Oncol*; 24(13):20e-22e.
- Lamers CH, Willemsen R, van Elzakker P, et al (2011) Immune responses to transgene and retroviral vector in patients treated with ex vivo-engineered T cells. *Blood*; 117(1):72-82.
- Lee D, Gardner R, Porter DL, et al (2014) Current concepts in the diagnosis and management of cytokine release syndrome. *Blood*; 124 (2): 188-195.
- Lee L, Wang L, Crump M (2011) Identification of potential surrogate end points in randomized clinical trials of aggressive and indolent non-Hodgkin lymphoma: correlation of complete response, time-to-event and overall survival end points. *Ann Oncol*; 22(6):1392–1403.
- Lenz G, Wright G, Dave SS, et al (2008) Stromal gene signatures in large-B-cell lymphomas. *N Engl J Med*; 359:2313–2323.
- Lenz G, Wright GW, Emre NC, et al (2008) Molecular subtypes of diffuse large B-cell lymphoma arise by distinct genetic pathways. *Proc Natl Acad Sci USA*; 105(36):13520-13525.

- Limsuwan T, Demoly P (2010) Acute symptoms of drug hypersensitivity (urticaria, angioedema, anaphylaxis, anaphylactic shock). *Med Clin North Am*; 94(4):691-710.
- Locke F, Neelapu S, Bartlett N, et al (2017) Pivotal Phase 2 Trial of Kte-C19 (anti-CD19 CAR T Cells) in Patients with Refractory Aggressive NHL (ZUMA-1). Presented at the 2017 BMT Tandem Meetings. Available from: <https://bmt.confex.com/tandem/2017/meetingapp.cgi/Paper/9822>, Accessed on 08/Mar/2017.
- Maher J, Brentjens R, Gunset G, et al (2002) Human T-lymphocyte cytotoxicity and proliferation directed by a single chimeric TCR zeta/ CD28 receptor. *Nat Biotechnol*; 20:70-75.
- Maude SL, Frey N, Shaw PA, et al (2014) Chimeric antigen receptor T cells for sustained remissions in leukemia. *N Engl J Med*; 371(16):1507-17.
- Maus MV, Grupp SA, Porter DL, et al (2014) Antibody-modified T cells: CARs take the front seat for hematologic malignancies. *Blood*, 123, 2625–35.
- Mehta S, Sastry BK, Souza R, et al (2017) Macitentan Improves Health-Related Quality of Life for Patients With Pulmonary Arterial Hypertension: Results From the Randomized Controlled SERAPHIN Trial. *Chest*. 2017 Jan;151(1):106-118.
- Mellman I, Coukos G, Dranoff G (2011) Cancer immunotherapy comes of age. *Nature*; 480(7378):480-9.
- Milone MC, Fish JD, Carpenito C, et al (2009) Chimeric receptors containing CD137 signal transduction domains mediate enhanced survival of T cells and increased antileukemic efficacy in vivo. *Mol Ther*; 17(8):1453-1464.
- Mohanlal R, Qiu Y, Zheng M, et al (2016) Long-Term Safety Follow-Up of Subjects Previously Treated with Non-Replicating Retroviral Vector-Based Gene Therapies. *Mol Diagn Ther*; 20(6):591-602.
- Moller MB, Christensen BE, Pedersen NT (2003) Prognosis of localized diffuse large B-cell lymphoma in younger patients. *Cancer*; 98(3):516-521.
- Mols F, Aaronson NK, Vingerhoets AJ, et al (2007) Quality of life among long-term non-Hodgkin lymphoma survivors: a population-based study. *Cancer* 109(8):1659–1667.
- Moskowitz C, Nimer S, Glassman J, et al (1999) The International Prognostic Index predicts for outcome following autologous stem cell transplantation in patients with relapsed and primary refractory intermediate-grade lymphoma. *Bone Marrow Transplant*; 23(6):561-7.
- Mounier N, El Gnaoui T, Tilly H, et al (2013) Rituximab plus gemcitabine and oxaliplatin in patients with refractory/relapsed diffuse large B-cell lymphoma who are not candidates for high-dose therapy. A phase II lymphoma study association trial. *Haematologica*; 10.3324/haematol.2013.090597.
- Mueller SM, Ege M, Pottharst A, et al (2001) Transplacentally acquired maternal T lymphocytes in severe combined immunodeficiency: a study of 121 patients *Blood*;98 (6): 1847-51.
- Mughal T, Ejaz AA, Foringer JR, et al (2010) An integrated clinical approach for the identification, prevention, and treatment of tumor lysis syndrome. *Cancer Treat Rev*; 36(2):164-76.

Mullaney BP, Pallavicini MG (2001) Protein-protein interactions in hematology and phage display. *Exp Hematol*; 29(10):1136-1146.

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) - B-cell Lymphomas, Guidelines Version 7.2018 (2018).

Neelapu S, Tummala S, Kebriaei P, et al (2017) Chimeric Antigen Receptor T-cell Therapy – assessment and management of toxicities. *Nature*; advance online publication 1-16.

Oerlemans S, Mols F, Nijziel M, et al (2011) The impact of treatment, socio-demographic and clinical characteristics on health-related quality of life among Hodgkin's and non-Hodgkin's lymphoma survivors: a systematic review. *Ann Hematol*; 90:993–1004.

Palmer DC, Balasubramaniam S, Hanada KI, et al (2004) Vaccine-Stimulated, Adoptively Transferred CD8⁺ T Cells Traffic Indiscriminately and Ubiquitously while Mediating Specific Tumor Destruction. *J Immunol*; 173(12):7209-7216.

Park JR, Digiusto DL, Slovak M, et al (2007) Adoptive transfer of chimeric antigen receptor re-directed cytolytic T lymphocyte clones in patients with neuroblastoma. *Mol Ther*; 15:825-833.

Persons DA, Baum C (2011) Solving the problem of γ -retroviral vectors containing long terminal repeats. *Mol Ther*; 19(2):229-231.

Pinthus JH, Waks T, Kaufman-Francis K, et al (2003) Immuno-gene therapy of established prostate tumors using chimeric receptor-redirected human lymphocytes. *Cancer Res*; 63:2470-2476.

Porter DL, Levine BL, Kalos M, et al (2011) Chimeric antigen receptor-modified T cells in chronic lymphoid leukemia. *N Engl J Med*; 365(8):725-733.

Pule M, Finney H, Lawson A (2003) Artificial T-cell receptors. *Cytotherapy*; 5(3):211-226.

Russell JA, Walley KR, Singer J, et al (2008) Vasopressin versus norepinephrine infusion in patients with septic shock. *N Engl J Med*; 358(9):877-887.

Sadelain M, Riviere I, Brentjens R (2003) Targeting tumours with genetically enhanced T lymphocytes. *Nat Rev Cancer*; 3:35-45.

Sant M, Allemani C, Tereanu C (2010) Incidence of hematologic malignancies in Europe by morphologic subtype: results of the HAEMACARE project. *Blood*; 116(19):3724-3734.

Sarkozy C, Coiffier B (2015) Primary refractory diffuse large B cell lymphoma in the rituximab era. *Curr Opin Oncol*; 27:377-383.

Schuster SJ, Bishop MR, Tam CS, et al (2017) Primary Analysis of Juliet: A Global, Pivotal, Phase 2 Trial of CTL019 in Adult Patients with Relapsed or Refractory Diffuse Large B-Cell Lymphoma. Oral presented at ASH 2017; Atlanta.

Schuster SJ, Svoboda J, Chong EA, et al (2017) Chimeric Antigen Receptor T Cells in Refractory B-Cell Lymphomas. *NEJM*; 377:2545-2554.

Sehn LH, Chua N, Mayer J, et al (2016) Obinutuzumab plus bendamustine versus bendamustine monotherapy in patients with rituximab-refractory indolent non-Hodgkin Lymphoma (GADOLIN): a randomised, controlled, open-label, multicentre, phase 3 trial. *Lancet Oncol*; 17(8):1081-93.

- Sehn LH, Goy A, Offner FC, et al (2015) Randomized Phase II Trial Comparing Obinutuzumab (GA101) With Rituximab in Patients With Relapsed CD20+ Indolent B-Cell Non-Hodgkin Lymphoma: Final Analysis of the GAUSS Study. *J Clin Oncol*; 33(30):3467-74.
- Shi Q, Schmitz N, Flowers C, et al (2016) Evaluation of Progression-Free Survival (PFS) As a Surrogate Endpoint for Overall Survival (OS) in First-Line Therapy for Diffuse Large B-Cell Lymphoma (DLBCL): Findings from the Surrogate Endpoint in Aggressive Lymphoma (SEAL) Analysis of Individual Patient Data from 7507 Patients. *Blood*; 128:4196 A.
- Siegel RL, Miller KD, Jemal A (2017) Cancer statistics, 2017. *CA Cancer J Clin*; 67(1):7-30.
- Skaper SD, Facci L, Giusti P (2014) Neuroinflammation, Microglia and Mast Cells in the Pathophysiology of Neurocognitive Disorders. *CNS & Neurological Disorders - Drug Targets*; 13:1654-1666.
- Stein S, Ott MG, Schultze-Strasser S, et al (2010) Genomic instability and myelodysplasia with monosomy 7 consequent to EVI1 activation after gene therapy for chronic granulomatous disease. *Nat Med*; 16(2):198-204.
- Surh CD, Sprent J (2000) Homeostatic T cell proliferation: how far can T cells be activated to self-ligands? *J Exp Med*; 192(4):F9-F14.
- Swerdlow SH, Campo E, Pileri SA, et al (2016) The 2016 revision of the World Health Organization classification of lymphoid neoplasms. *Blood*; 127(20):2375-90.
- Swigris JJ, Brown KK, Behr J, et al (2010) The SF-36 and SGRQ: Validity and first look at minimum important differences in IPF. *Respir Med* 104: 296-304.
- Teachey DT, Bishop MR, Maloney DG, et al (2018) Toxicity Management after chimeric antigen receptor T cell therapy: one size does not fit 'ALL'. *Nat Rev Clin Oncol* 15: 218.
- Tesfa D, Palmblad J (2011) Late-onset neutropenia following rituximab therapy: incidence, clinical features and possible mechanisms. *Expert Rev Hematol*; 4(6):619-25.
- Tey SK (2014) Adoptive T-cell therapy: adverse events and safety switches. *Clin Transl Immunology*; 3(6):e17.
- Tilly H, Gomes da Silva M, Vitolo U, et al (2015) Diffuse large B-cell lymphoma (DLBCL): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up: on behalf of the ESMO Guidelines Committee. *Annals of Oncology*; 26(Suppl 5):v116–v125.
- Turtle CJ, et al (2015) Addition of Fludarabine to Cyclophosphamide Lymphodepletion Improves In Vivo Expansion of CD19 Chimeric Antigen Receptor-Modified T Cells and Clinical Outcome in Adults with B Cell Acute Lymphoblastic Leukemia. *Blood*; 126:3773.
- Turtle CJ, Hay KA, Hanafi LA, et al (2017) Durable Molecular Remissions in Chronic Lymphocytic Leukemia Treated With CD19-Specific Chimeric Antigen Receptor-Modified T Cells After Failure of Ibrutinib. *J Clin Oncol*; 35(26):3010-3020.
- Van den Neste E, Schmitz N, Mounier N, et al (2016) Outcome of patients with relapsed diffuse large B-cell lymphoma who fail second-line salvage regimens in the International CORAL study. *Bone Marrow Transplantation*; 51:51–57.
- Van den Neste E, Schmitz N, Mounier N, et al (2017) Outcomes of diffuse large B-cell lymphoma patients relapsing after autologous stem cell transplantation: an analysis of patients included in the CORAL study. *Bone Marrow Transplantation*; 52: 216–221.

Van Imhoff GW, McMillan A, Matasar MJ, et al (2017) Ofatumumab Versus Rituximab Salvage Chemoimmunotherapy in Relapsed or Refractory Diffuse Large B-Cell Lymphoma: The ORCHARRD Study. *J Clin Oncol*; 35(5): 544-551.

Van Stipdonk MJ, Lemmens EE, Schoenberger SP (2001) Naïve CTLs require a single brief period of antigenic stimulation for clonal expansion and differentiation. *Nat Immunol*; 2(5):423-429.

Velasquez WS, Cabanillas F, Salvador P, et al (1998) Effective salvage therapy for lymphoma with cisplatin in combination with high-dose Ara-C and dexamethasone (DHAP). *Blood*; 71:117–122.

Ware JE, Sherbourne CD (1992) The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care*; 30(6):473-483.

Webster K, Cella D, Yost K (2003) The Functional Assessment of Chronic Illness Therapy (FACIT) Measurement System: properties, applications, and interpretation. *Health and Qual Life Outcomes*. 1; 79.

Zhou Z, Sehn LH, Rademaker AW, et al (2014) An enhanced International Prognostic Index (NCCN-IPI) for patients with diffuse large B-cell lymphoma treated in the rituximab era. *Blood*; 123(6):837-42.

16 Appendices

16.1 Appendix 1: Eligibility based on serologic markers for hepatitis B and C:

Table 16-1 Eligibility based on serologic marker for hepatitis B and C

Test	Result				
HBsAg	+	-	-	-	-
HBcAb	Any	+	-	+	-
HBsAb	Any	-	+	+	-
HCV Ab	Any	Any	-	-	-
Eligibility	Not Eligible	Not Eligible	Eligible	Eligible	Eligible

If indeterminate results are obtained, viral DNA (hepatitis B) or RNA (hepatitis C) should be measured to confirm negative viral status.

HBsAg positive: Indicates active infection and risk for reactivation with fulminant hepatitis. These subjects are not eligible for this trial.

HBcAb positive: As a standalone marker, it indicates active infection and risk for reactivation. These subjects are not eligible for this trial.

HBsAb positive: As a standalone marker, it indicates successful vaccination or previous infection that has been successfully resolved if the only positive finding. These subjects are eligible for this trial.

HBsAg negative, HBcAb positive, HBsAb positive: Resolved or latent infection. These subjects are eligible for this trial, however, they are at risk for viral reactivation (see Kymriah label, Warnings and Precautions).

HCV Ab positive: Indicates active infection and risk for reactivation. These subjects are not eligible for this trial.

All markers negative: No prior exposure or vaccination to hepatitis B and no prior exposure to Hepatitis C. Subjects are eligible for this trial.

16.2 Appendix 2: Guidelines for efficacy evaluation in non-Hodgkin-Lymphoma studies

16.2.1 Introduction

The purpose of this document is to provide working definitions and rules to evaluate efficacy in non-Hodgkin lymphoma (NHL) studies conducted by Novartis. This document is based on the International Working Group response criteria ([Cheson et al 1999](#)), the International Harmonization Project revised response criteria ([Cheson et al 2007](#)), and the revised Consensus of the International Conference on Malignant Imaging Working Group and the Lugano Classification ([Barrington et al 2014](#); [Cheson et al 2014](#)), and it is intended for studies of radiographically measurable disease. For studies without measurable disease, e.g., studies of consolidation of complete response, maintenance treatment, or autologous stem cell transplantation, see [Appendix A](#).

16.2.2 Methodologies

16.2.2.1 Computed tomography (CT)

The same method of assessment and technique should be used to characterize each identified and reported lesion throughout the study. Contrast-enhanced CT of neck, chest, abdomen and pelvis, from skull base through lesser trochanters ensuring complete coverage of the pelvis and inguinal areas, should be performed using a ≤ 5 mm slice thickness with a contiguous reconstruction algorithm. If a patient has a CT contrast allergy or develops it during the trial, non-contrast CT of the chest plus contrast-enhanced MRI of abdomen and pelvis are acceptable for a follow up. Chest MRI is not recommended due to respiratory artifacts.

16.2.2.2 Positron emission tomography (PET)

Studies of FDG-avid histologies require PET using the radiotracer ^{18}F -fluorodeoxyglucose (FDG) to confirm any new CR determined by CT. PET will not be required to confirm progression or relapse.

PET scans should cover the whole body from base of skull to mid-thigh. Examinations should be consistent across all time points including amount of tracer, location of injection, arm location, and scan delay. Information of height, weight, gender, administered dose, time between dose administration and imaging, and glucose level are required for each time point. PET images should be converted to standardized uptake value (SUV) maps to support comparison across time points and to standardize viewing conditions.

16.2.2.3 PET-CT

Hybrid PET-CT may be used to acquire PET and CT images if CT images produced by the scanner are of diagnostic quality and include intravenous contrast. Non-diagnostic CT images acquired for attenuation purposes during PET-CT are NOT acceptable as the only images for the time point.

If diagnostic CT and PET are to be acquired on the same day, PET must be performed prior to CT with IV contrast to avoid compromising PET results.

Thus, any of the three following imaging methodologies are possible in a lymphoma study:

- PET-CT with diagnostic CT
- PET-CT with non-diagnostic CT and dedicated diagnostic CT
- Dedicated diagnostic CT and dedicated FDG PET

16.2.2.4 Magnetic resonance imaging (MRI) and PET-MRI

MRI or PET-MRI is an acceptable method of imaging if CT is contraindicated e.g., due to CT contrast allergy. If at baseline a patient is known to be allergic to CT contrast or develops allergy during the trial, the following change in imaging modality will be accepted for follow up: a non-contrast CT of the chest plus contrast-enhanced MRI of abdomen and pelvis (MRI of the chest is not recommended due to respiratory artifacts).

16.2.2.5 Five point scale (5PS)

To standardize PET interpretation, a simple reproducible scoring method called the five point scale (5PS) or the Deauville criteria has been implemented for initial staging and assessment of interim and end of treatment responses ([Barrington et al 2014](#)). The 5PS assesses the most intense uptake in a site of disease ([Table 16-2](#)).

Table 16-2 **Five Point Scale (5PS)**

Score	Findings
Score 1	No uptake above background
Score 2	Uptake ≤ mediastinum
Score 3*	Uptake > mediastinum, but ≤ liver
Score 4**	Uptake moderately > liver
Score 5**	Uptake markedly higher than liver and/or new lesions
* The protocol will need to define the significance of a score 3, depending on the studied disease, patient characteristics and goal of therapy.	
• Score 3 will be considered PET negative unless otherwise specified in the protocol (e.g. de-escalation studies, in which case CMR will be based on 5PS of 1 or 2 only, and PMR/NMR/PMD will be based on 5PS of 3,4 or 5)	
** Score 4 should be applied to uptake greater than the maximum standard uptake value (SUV) in a large region \ of normal liver and score 5 to uptake 2 times greater than the maximum SUV in the liver. PET images should be converted to SUV maps to support comparison across time points and to standardize viewing conditions.	
(New) areas of uptake unlikely to be related to lymphoma will be marked as “X” (Barrington et al. 2014).	

16.2.3 Definitions

16.2.3.1 Disease stage

Extent and involvement by lymphoma is described by the disease stage and is an important prognostic factor. Stage can also influence treatment decisions.

16.2.3.2 Baseline

Baseline examination should be as close as possible to the randomization/start of treatment (e.g., within 4 weeks prior to randomization/start of treatment). Longer periods may be allowed depending on the disease studied and the study design.

16.2.3.3 Nodal vs. extranodal lesion

A lesion can be categorized as:

- Nodal lesion (a lymph node or a nodal mass)
- Extranodal lesion (a lesion located in other organs, including spleen and liver)

16.2.3.4 Measurable disease

All anatomic measurements should be taken in two perpendicular dimensions and recorded in metric notation, using a ruler or calipers.

Throughout this document, a lesion will be called measurable if:

- It can be measured accurately in two perpendicular dimensions: longest diameter (LDi) (also known as transverse diameter), and shortest diameter (SDi), which is the longest diameter perpendicular to LDi (also known as perpendicular diameter). The LDi and SDi must be measured on the same slice.
- For a nodal lesion, LDi is greater than 15 mm, regardless of SDi
- For an extranodal lesion, if both LDi and SDi are greater than 10 mm

A lymph node not meeting the measurability criteria but with LDi greater than 15 mm (e.g. SDi cannot be measured accurately) will constitute a non-measurable nodal lesion if FDG-avid (for FDG-avid histologies).

A lymph node not meeting the measurability criteria but with LDi ranging from 11 mm to 15 mm and with SDi greater than 10 mm will be checked for relationship to disease as follows:

- If it is related to lymphoma, it will constitute a non-measurable nodal lesion (referred to as “involved node” in [Cheson et al \(2007\)](#))
- If not related to lymphoma and not FDG-avid, it will constitute an abnormal lymph node but not a nodal lesion for FDG-avid histologies

All lesions visible on PET but not on CT/MRI will be treated as non-measurable.

Bulky disease

Bulky disease is captured by means of the longest measurement by CT scan. The definition of bulky disease (a minimum size) should be included in the study protocol.

16.2.3.5 Assessable disease

Assessable disease refers to disease presentations that are consistent with lymphoma but are not suitable for measurement, e.g., pleural effusion, ascites, etc. Assessable disease will be followed qualitatively.

16.2.3.6 Index lesion

- Up to 6 of the largest nodes, nodal masses or other lymphomatous lesions, including extranodal lesions, measurable in two diameters (LDi and SDi)
- Should represent overall disease burden and include mediastinal and retroperitoneal disease, if involved

16.2.3.7 Non-index lesion

- All other lesions which are not selected as index lesions but are consistent with lymphoma
- Abnormal nodes and extranodal lesions, both measurable and non-measurable, such as cutaneous, gastrointestinal, and bone lesions, pleural or pericardial effusions, and ascites

16.2.3.8 New lesions

- Regrowth of previously resolved lesions
- A new nodal lesion > 15 mm in any axis
- A new extranodal lesion > 10 mm in any axis
- A new extranodal lesion ≤ 10 mm in any axis that is unequivocal and attributable to lymphoma
- A new assessable lesion attributable to lymphoma (e.g., ascites, pleural effusion)

16.2.4 Efficacy assessments

16.2.4.1 Eligibility

In general, patients should have at least one measurable nodal lesion (greater than 15 mm in the long axis) or at least one measurable extranodal lesion (with both LDi and SDi greater than 10 mm).

16.2.4.2 Methods of disease assessment

16.2.4.2.1 PET combined with diagnostic CT

The integration of PET into more frequently acquired CT evaluation does present a challenge to the way response is assessed in a clinical trial. The study protocol must clearly define the imaging intervals and imaging methods to be used at each imaging visit. PET scans should be performed at pre-specified times for example at randomization before treatment and at clearly defined times during and/or after the end of treatment. PET may also be acquired to confirm CT results.

The same CT imaging modality should be used at baseline and all post-baseline assessments in order to reduce the risk of false responses or progressions based on measurement error. A change in modality can be either a change in contrast use (i.e., with contrast versus without contrast) or a change in technique (e.g. from CT to MRI). Response assessments made after a change in imaging modality should be queried, and if the investigator or blinded central reviewer can provide sufficient justification, then the response can be accepted.

In order to calculate the sum of the product of the perpendicular diameters (PPD) of all index lesions, their size must be recorded throughout the study. Actual lesion measurements should be entered on the corresponding CRFs. If, during the course of the study, either of the perpendicular diameters of a lesion cannot be reliably measured because of its small size, it is recommended to enter the minimum limit of detection as the diameter size (e.g., 5 mm for spiral CT). In other cases when, during the course of the study, the diameter cannot be reliably measured for reasons other than its size (i.e., borders of the lesion are confounded by

neighboring anatomical structures), no measurement should be entered and the lesion cannot be evaluated.

If lesions become confluent over time, it is recommended to measure them as one lesion, report the overall diameters to one of the lesions and assign 0 mm × 0 mm to each of the other previously measured lesions. The PPD of the current confluent mass should be used to measure response, with more than 50% increase in the PPD of the confluent mass compared with nadir of the sum of individual nodes necessary to indicate progressive disease.

If a lesion splits into several discrete lesions, the individual product of the perpendicular diameters (PPDs) of each lesion should be summed together to represent the PPD of the split lesion; this PPD is added to the sum of the PPDs of the remaining lesions to measure response. If subsequent growth of any or all of these discrete nodes occurs, the nadir of each individual node is used to determine progression (as if each individual node was selected as an index lesion at baseline).

16.2.4.2.2 Bone marrow assessment

Bone marrow should be evaluated by biopsy or aspirate in all patients at baseline. If lymphoma involvement in bone marrow is observed at baseline, then biopsy or aspirate should be performed post-baseline to confirm radiological CR. Any deviation from this approach should be justified in the study protocol.

16.2.4.2.3 Physical examination

Skin lesions must be histologically confirmed for lymphoma involvement (the investigational site must document the histological confirmation (yes or no) on the corresponding CRF) and photographed including a ruler (color photography using digital camera). Response assessment of skin lesions will be performed and results will be recorded on the corresponding CRF at baseline and at the time of each radiological assessment.

16.2.4.3 Documentation of disease

For the evaluation of disease at baseline and throughout the study, the following will be recorded.

16.2.4.3.1 FGD uptake

FDG uptake in a nodal or extranodal site that is suggestive of lymphoma will be assessed using 5PS.

16.2.4.3.2 Index lesions

A minimum of one measurable index lesion and a maximum of six of the largest dominant nodal and extranodal lesions must be documented at baseline and assessed throughout the study in two dimensions. The lesions should come from different body regions representative of the patient's overall disease burden and should include mediastinal and retroperitoneal disease, if involved. Two perpendicular dimensions (LDi, SDi) must be recorded on the corresponding CRF at each assessment of a measurable lesion selected to be an index lesion.

Index nodal lesions

Index nodal lesions are selected from the measurable nodal lesions and should be documented at baseline and assessed throughout the study. Index nodal lesions should be from disparate regions of the body including mediastinal and retroperitoneal areas of disease whenever these sites are involved.

Index extranodal lesions

Other organs such as breast and lung can be occasionally involved by lymphoma. Such extranodal lesions (e.g. hepatic nodules) may be included (if measurable) in the six index lesions to be assessed throughout the study. In some cases histological examination may be necessary to confirm that these lesions represent lymphoma involvement (e.g. skin lesions).

16.2.4.3.3 Non-index lesions

Non-index nodal lesions

Nodal lesions not selected as index lesions (both measurable and non-measurable) are considered as non-index lesions. Non-index lesions should be documented at baseline and assessed throughout the study. Measurements of these lesions are not required to be documented on the CRF.

Non-index extranodal lesions

Measurable extranodal lesions not selected as index lesions and all non-measurable extranodal lesions (including non-measurable but assessable disease e.g. pleural effusion) will be documented at baseline and assessed throughout the study as non-index lesions. Measurements of these lesions are not required to be documented on the CRF.

16.2.4.3.4 Spleen involvement

Splenic involvement is determined by imaging: vertical (cranial to caudal) length > 13 cm is considered as involved, and spleen length must be assessed at each imaging time point. Intrasplenic lesions should be followed as index, non-index and new extranodal lesions.

16.2.4.3.5 Liver involvement

Given variability in physical habitus and the impact of numerous medical conditions, assessment of liver size is not considered a reliable measure of hepatic involvement and therefore liver assessment is not included in the Lugano 2014 classification. Intrahepatic lesions should be followed as index, non-index and new extranodal lesions.

16.2.4.3.6 Bone marrow involvement

Lymphoma involvement in bone marrow should be documented in the CRF as “Yes” or “No” at each bone marrow biopsy and/or aspiration.

16.2.4.4 Response evaluation

The efficacy variables in the statistical analysis are based on **overall disease response**, which is a combined evaluation of response based on both radiological and clinical findings, and is

determined at each post-baseline assessment. The radiological response is first obtained from CT and PET studies according to the Lugano criteria (Table 16-2) and overall disease response is then determined by taking into account results of bone marrow biopsies and other clinical information (Table 16-3).

16.2.4.4.1 Radiological response

There are three separate components to radiological response, all of which should be collected on the CRF at each post-baseline assessment:

1. **CT response** based on anatomical measurements of index/non-index/new lesions and spleen length. The possible response outcomes are complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD) as defined in Table 16-3.
2. **PET response** based on 5PS, changes in intensity or extent of standard uptake values (SUVs) and bone marrow assessments directly from the PET scan. The possible outcomes for PET response are complete metabolic response (CMR), partial metabolic response (PMR), no metabolic response (NMR), or progressive metabolic disease (PMD) as defined in Table 16-3.
3. **Overall radiological response** combines CT response with PET response. The outcomes include CR, PR, SD, and PD. For time points when both CT and PET are available, PET response overrules CT response. Overall radiological response at a time point with CT only may also be affected by PET response obtained at a different time point.

Example

A CT response of PR at the same assessment as a PET response of CMR will constitute an overall radiological response of CR, and (i) a subsequent time point with CT only and CT response of PR will still constitute an overall radiological response of CR, (ii) a previous time point with CT only and CT response of PR may be upgraded to CR at the discretion of the investigator or blinded central reviewer.

Table 16-3 Radiological response assessment

		PET-based response	CT-based response
		Complete Metabolic Response (CMR) (All of the following)	Complete Response (CR) (All of the following)
Complete Response	Index	5PS [†] of 1, 2, or 3* with or without residual mass on 5PS	Nodal lesion: ≤ 15 mm in Ldi
	Non-index		Extranodal lesion: Absent (0 mm x 0 mm)
	Spleen		Absent
	New lesions	None	Return to normal (≤ 13 cm)
	Bone marrow	No FDG-avid disease	None
		Partial Metabolic Response (PMR) (all of the following)	Partial Response (PR) (all of the following)
Partial Response	Index	5PS of 4 or 5 with reduced uptake compared to baseline with respect to SUV intensity or extent. This may apply	≥ 50% decrease from baseline in SPD across all index lesions
	Non-index		No increase

	Spleen	to the specific hot spot and/ or overall the subject. It is expected that there will be residual mass(es) present.	≥ 50% decrease from baseline in enlarged portion of spleen <i>Example: If 16 cm, then enlarged portion is 3 cm. A decrease by 2 cm gives a 66.6% decrease</i>
	New lesions	None	None
	Bone marrow	<ul style="list-style-type: none"> Residual uptake higher than uptake in normal marrow but reduced compared with baseline Persistent focal changes in the marrow with nodal response 	Not applicable
		No Metabolic Response (NMR) (all of the following)	Stable Disease (SD) (all of the following)
Stable Disease	Index	5PS of 4 or 5 with no significant change in FDG uptake from baseline	<ul style="list-style-type: none"> <50% decrease from baseline in SPD across all index lesions No criteria for PD are met
	Non-index		No progression
	Spleen		No progression
	New lesions	None	None
	Bone marrow	No change in FDG uptake from baseline	Not applicable
		Progressive Metabolic Disease (PMD) (At least one of the following)	Progressive Disease (PD) (At least one of the following)
Progressive Disease	Index	5PS of 4 or 5 with increased uptake compared to the visually determined nadir with respect to SUV intensity or extent. This may apply to the specific hot spot and/ or overall the subject. and/or <ul style="list-style-type: none"> New FDG-avid foci consistent with lymphoma Consider biopsy or interval scan if etiology of new lesions uncertain 	PPD Progression [#] : An individual node/lesion must be abnormal with: <ul style="list-style-type: none"> LDi > 15 mm AND Increase by ≥ 50% from PPD nadir AND An increase in LDi or SDi from nadir: ≥ 5 mm for lesions with LDi ≤ 20 mm at current assessment ≥ 10 mm for lesions with LDi > 20 mm at current assessment
	Non-index		Unequivocal Progression
	Spleen		<ul style="list-style-type: none"> Progression (increase from baseline by >50% in enlarged portion). <i>Example: If 15 cm at baseline then enlarged portion is 2 cm and an increase by >1 cm would be progression</i> New splenomegaly (> 13 cm and increase by > 2 cm from normal at baseline) Recurrent splenomegaly (normalization followed by increase by > 2 cm from nadir reaching > 13 cm)

	New lesions		<ul style="list-style-type: none"> Regrowth of previously resolved lesions New node > 15 mm in any axis New extranodal site > 10 mm in any axis New extranodal site ≤ 10 mm in LD_i, unequivocal and attributable to lymphoma Assessable disease of any size Unequivocally attributable to Lymphoma
	Bone marrow	New/recurrent FDG-avid foci	Not applicable

Abbreviations: LD_i Longest diameter; SD_i Shortest diameter; PPD Product of perpendicular diameters; SPD Sum of the product of the perpendicular diameters.

* Score 3 will be considered PET negative unless otherwise specified in the protocol (e.g. de-escalation studies, in which case CMR will be based on 5PS of 1 or 2 only, and PMR/NMR/PMD will be based on 5PS of 3, 4 or 5)

In the context of an agent associated with a flare reaction, caution must be exercised not to confuse the possible tumor flare with progressive disease. It is recommended that either a biopsy be performed or the lesion be reassessed in at least 2 weeks, and if there is continued evidence of tumor progression, the date of progressive disease is the previous evaluation.

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

16.2.4.4.2 Overall disease response

Overall disease response is determined by assessing whether the combined radiological responses at each time point are appropriate, based on bone marrow biopsies and other clinical findings that may be available, such as cytology results, physical examination results of palpable lesions or skin lesions, and biopsies of lymph nodes or extra-nodal lesions (Table 16-4). The possible outcomes for overall disease response are CR, PR, SD, and PD.

For example, suppose there was lymphoma involvement in the baseline bone marrow biopsy, and the month 3 combined radiological response was CR (implying that PET-based bone marrow involvement at month 3 was negative). In that case, overall disease response could only be CR if there was a negative bone marrow biopsy otherwise overall disease response would be downgraded to PR. This is a case where the bone marrow biopsy results overrule the bone marrow findings on PET. Another example is when the combined radiological response is SD, but cytology results of a pleural effusion show lymphoma involvement: this could lead to an overall disease response of PD.

Overall disease response at each post-baseline assessment should be captured on the CRF, along with the date of response. In addition, the source of any clinical data that affected the overall disease response should be documented.

Table 16-4 Overall disease response

Overall radiological response	Bone marrow biopsy/aspirate	Clinical findings	Overall disease response
CR/PR/SD	Negative at baseline or negative \pm 28 days from assessment	Any except new or recurrent lymphoma involvement	CR/PR/SD
CR	Positive at baseline and either positive (without new or recurrent involvement) or not done \pm 28 days from assessment	Any except new or recurrent lymphoma involvement	PR
PR/SD	Positive at baseline and either positive (without new or recurrent involvement) or not done \pm 28 days from assessment	Any except new or recurrent lymphoma involvement	PR/SD
PD	Any	Any	PD
Any	New or recurrent involvement	Any	PD
Any	Any	New or recurrent lymphoma involvement	PD

16.2.4.5 Efficacy analysis definitions

16.2.4.5.1 Best overall response

The best overall response (BOR) is the best overall disease response recorded from randomization/start of treatment until progressive disease or start of new anticancer therapy, whichever comes first. The definition of new anticancer therapy may need to be defined in the study protocol (e.g., high-dose chemotherapy with autologous stem cell transplantation).

A patient will have a best overall response of CR if they have CR as overall disease response for at least one of the assessments.

A patient will have a best overall response of PR if at least one overall disease response of PR is available (and the patient does not qualify for CR).

A best overall response of SD will be declared when at least one overall disease response of SD is available at least 6 weeks after randomization/start of treatment (and the patient does not qualify for CR or PR). If SD is observed before this minimum follow-up period, and the patient does not qualify for CR, PR or PD, then the best overall response would be unknown (UNK). If a different minimum follow-up period for SD is more appropriate (e.g., if first post-baseline visit is at 28 days) then this must be specified in the Study Protocol.

A patient will have a best overall response of PD if overall disease response is PD between randomization/start of treatment and the second scheduled post-baseline assessment (and the patient does not qualify for CR, PR or SD).

For example, assuming 12 weeks between assessments and a permitted variation in visit timing of \pm 1 week, this would mean during the first 25 weeks after randomization/start of treatment. If PD is observed after this maximum follow-up period, and the patient does not

qualify for CR, PR or SD, then the best overall response would be UNK. If a different maximum follow-up period for PD is more appropriate then this must be specified in the Study Protocol.

A patient will have a best overall response of UNK if the patient does not qualify for CR, PR, SD or PD.

Overall disease response at a given assessment may be provided from different sources:

- Per Investigator: overall disease response based on local radiological assessments, using investigator choice of index lesions, measurements and assessments of lesion status and 5PS along with clinical findings
- Per Central Blinded Review, with or without blinded adjudication: based on central review of local radiological assessments, using central reviewer choice of index lesions, measurements and assessments of lesion status and 5PS, along with clinical findings

In studies that include a central blinded review, the Study Protocol should state which source will be used for the primary analysis.

Best overall response is summarized by calculating the **overall response rate (ORR)**, which is defined as the proportion of patients with a best overall response of CR or PR.

Similarly, the complete response rate is the proportion of patients with a best overall response of CR.

16.2.4.5.2 Time to event variables

Most of the time to event variables are defined in this section according to the revised International Working Group response criteria ([Cheson et al 2007](#)). Further details on dates and censoring rules are provided respectively in [Section 16.2.4.5.3](#) and [Section 16.2.4.5.4](#).

Overall survival

Overall survival (OS) is defined as the time from the date of randomization/start of treatment to the date of death due to any cause. If a patient is not known to have died, OS will be censored at the date of last contact.

Progression-free survival

Progression-free survival (PFS) is defined as the time from the date of randomization/start of treatment to the date of event defined as the first documented progression (overall disease response = PD) or death due to any cause. If a patient has not had an event, PFS is censored at the date of the last adequate assessment as defined in [Section 16.2.4.5.3](#).

Time to progression

Time to progression (TTP) is defined as the time from the date of randomization/start of treatment to the date of first documented progression (overall disease response = PD) or death due to lymphoma. If a patient has not had an event, TTP is censored at the date of the last adequate assessment.

Duration of response

Duration of response (DOR) applies only to patients with best overall disease response of CR or PR. It is defined as the time from the date of the first documented overall disease response of CR or PR to the date of first documented progression or death due to lymphoma. If a patient has not had an event, DOR is censored at the date of the last adequate assessment. It should be stated that this analysis might introduce a bias as it includes only responders.

Duration of complete response applies only to patients with best overall disease response of CR. It is defined as the time from the date of the first documented overall disease response of CR to the date of first documented progression or death due to lymphoma. If a patient has not had an event, duration of CR is censored at the date of the last adequate assessment. Duration of CR might be calculated in addition for studies in which a reasonable number of complete responders are seen.

The analysis of DOR should only be used as a descriptive analysis. If used as an inferential comparison between treatments, clear justification must be given in the study protocol.

Time to response

Time to response (TTR) is defined as the time from the date of randomization/start of treatment to the date of first documented overall disease response of PR or CR. Depending on the study design, this analysis could be based on all patients only, or on responders only, or both of these analysis populations may be used. The choice of analysis population for TTR should be stated in the study protocol.

For analysis using all patients, TTR will be censored for patients who did not achieve a PR or CR:

- At maximum follow-up (i.e. FPFV to LPLV used for the analysis) for patients who had a PFS event (i.e. either progressed or died due to any cause)
- At the date of the last adequate assessment otherwise

Time to complete response (TTCR) is defined similarly to TTR except using CR only instead of either PR or CR, and with this difference, the above rules and definitions for TTR also apply to TTCR.

Lymphoma specific survival

Lymphoma specific survival (LSS) is defined as the time from the date of randomization/start of treatment to the date of death documented as a result of lymphoma. If a patient has not had an event, LSS will be censored:

- at the date of last contact if the patient is not known to have died
- at the date of death if the patient died for reason other than lymphoma

Event-free survival

Event-free survival (EFS) may be appropriate in studies of advanced disease where early discontinuation is typically related to intolerance of the study drug. In some protocols, EFS may be considered as a sensitivity analysis for TTP. If a patient has not had an event, EFS is censored at the date of the last adequate assessment as defined in [Section 16.2.4.5.3](#). The definition of event needs to be defined in the Study Protocol according to study design.

16.2.4.5.3 Definition of start and end dates for time to event variables

Assessment date

For each assessment, the assessment date is calculated as:

- the latest date of all radiological measurements (e.g. PET-CT, CT, or MRI), excluding bone marrow biopsy, if overall disease response at that assessment is CR/PR/SD/UNK
- the earliest date of all measurements (e.g. PET-CT, CT, or MRI), including bone marrow biopsy if overall disease response at that assessment is PD

Start date

For all “time to event” variables other than the duration of response variables, the date of randomization/start of treatment will be used as the start date.

For the calculation of duration of response variables the following start date should be used:

- Date of first documented response is the assessment date of the first overall disease response of CR for duration of complete response or CR/PR for duration of response

End date

The end dates which are used to calculate ‘time to event’ variables are defined as follows:

- Date of death as reported on the disposition CRF
- Date of last contact is defined as the last date the patient was known to be alive as derived from different CRF pages (see details in [Section 16.2.5.2](#))
- Date of progression is the first assessment date at which the overall disease response was recorded as PD
- Date of last adequate assessment is the date of the last assessment with overall disease response of CR, PR or SD which was made before an event or a censoring reason occurred. If no post-baseline assessments are available (before an event or a censoring reason occurred) the date of randomization/start of treatment is used.
- Date of next scheduled assessment is the date of the last adequate assessment plus the protocol specified time interval between assessments. This date may be used if back-dating is considered when the event occurred beyond the acceptable time window for the next radiological assessment as per protocol.

Example (if protocol defined schedule of assessments is 3 months): response assessments at baseline - 3 months - 6 months - missing - missing - PD. Date of next scheduled assessment would then correspond to 9 months.

- Date of treatment discontinuation is the last known date subject took study drug (*to be used, if applicable*)
- Date of new anti-cancer therapy is defined as the start date of first new antineoplastic therapy (including medication, radiotherapy, surgery or HSCT)

16.2.4.5.4 Censoring and sensitivity analyses

Censoring reasons

This section outlines the possible censoring reasons for each time to event variables. In order to summarize the various reasons for censoring, the following categories ([Table 16-5](#)) will be calculated for each time to event variable based on the information reported.

Table 16-5 Censoring reasons

Time to event variables	Possible censoring reasons
OS	<ul style="list-style-type: none"> • Alive • Lost to follow-up
PFS, EFS, TTP and DOR	<ul style="list-style-type: none"> • Ongoing without event • Lost to follow-up • Withdrew consent • Death due to reason other than lymphoma (only used for TTP and DOR) • New anti-cancer therapy added (except for EFS optional, see Table 16-6) • Event documented after two or more missing response assessments (optional, see Table 16-6) • Adequate assessment no longer available¹
LSS	<ul style="list-style-type: none"> • Alive • Lost to follow-up • Death due to reason other than lymphoma

¹ Adequate assessment is defined in [Section 16.2.4.5.3](#). This reason corresponds to any censoring reasons after two or more missing response assessments. This reason will also be used for censor in case of no baseline assessment

Event date, censoring date and sensitivity analyses

This section outlines the possible event and censoring dates for progression ([Table 16-6](#)), as well as addressing the issues of missing response assessments during the study. It is important that the protocol and analysis plan specify the primary analysis in detail with respect to the definition of event and censoring dates and also include a description of one or more sensitivity analyses to be performed.

Based on definitions outlined in [Section 16.2.4.5.2](#), and using the draft FDA guideline on endpoints ([FDA 2007](#)) as a reference, the following analyses can be considered:

Table 16-6 Options for event dates used in PFS, EFS, TTP, DOR

Situation		Options for end-date (progression) ¹ (1) = default unless specified differently in the protocol or analysis plan	Outcome
A	No baseline assessment	(1) Date of randomization/start of treatment ²	Censor
B	Progression at or before next scheduled assessment	(1) Date of progression (2) Date of next scheduled assessment ¹	Event Event
C1	Progression or death due to any reason after exactly one missing assessments	(1) Date of progression (or death) (2) Date of next scheduled assessment ¹	Event Event
C2	Progression or death due to any reason after two or more missing assessments	(1) Date of last adequate assessment ¹ (2) Date of next scheduled assessment ¹ (3) Date of progression (or death)	Censor Event Event
D	No progression	(1) Date of last adequate assessment	Censor
E	Treatment discontinuation due to 'Disease progression' without documented progression, i.e. clinical progression based on investigator claim	(1) N/A (2) Date of discontinuation (visit date at which clinical progression was determined)	Ignored Event
F	New anticancer therapy given (except for EFS, in which this is always an event)	(1) Date of last adequate assessment (2) Date of new anticancer therapy (3) Date of secondary anti-cancer therapy (4) N/A	Censor Censor Event Ignored
G	Death due to reason other than lymphoma	(1) Date of last adequate assessment	Censor (only TTP and DOR)
¹ = Definitions can be found in Section 16.2.4.5.3 . ² = The rare exception to this is if the patient dies no later than the time of the second scheduled assessment as defined in the protocol in which case this is a PFS event at the date of death.			

The primary analysis and the sensitivity analyses must be specified in the Study Protocol. Clearly define if and why options (1) are not used for situations C, E and (if applicable) F.

Situations C (C1 and C2): Progression or death after one or more missing assessments:

The primary analysis is usually using options (1) for situations C1 and C2, i.e.

- (C1) taking the actual progression or death date, in the case of only one missing assessment
- (C2) censoring at the date of the last adequate assessment, in the case of two or more consecutive missing assessments

In the case of two or missing assessments (situation C2), option (3) may be considered jointly with option (1) in situation C1 as sensitivity analysis. A variant of this sensitivity analysis consists of backdating the date of event to the next scheduled assessment as proposed with option (2) in situations C1 and C2.

Situation E: Treatment discontinuation due to 'Disease progression' without documented progression: By default, option (1) is used for situation E as patients without documented PD should be followed for progression after discontinuation of treatment. However, option (2) may be used as sensitivity analysis. If progression is claimed based on clinical deterioration instead of response assessment by e.g. CT-scan, option (2) may be used

for indications with high early progression rate or difficulties to assess the response due to clinical deterioration.

Situation F: New cancer therapy given (except for EFS): the handling of this situation must be specified in detail in the protocol. However, option (1), i.e. censoring at last adequate assessment may be used as a default in this case.

Additional suggestions for sensitivity analyses

Other suggestions for additional sensitivity analyses may include analyses to check for potential bias in follow-up schedules for response assessments, e.g.:

- By assigning the dates for censoring and events only at scheduled visit dates. The latter could be handled by replacing in [Table 16-6](#) the “Date of last adequate assessment” by the “Date of previous scheduled assessment (from baseline)”, with the following definition:

Date of previous scheduled assessment (from baseline) is the date when a response assessment would have taken place, if the protocol assessment scheme was strictly followed from baseline, immediately before or on the date of the last adequate assessment.

The need for these types of sensitivity analyses will depend on the requirements for a specific study and disease area and have to be specified in the Study Protocol or RAP documentation.

16.2.5 Data handling and programming conventions

The following rules should be used and specified in the RAP documentation:

16.2.5.1 Calculation of ‘time to event’ variables

Time to event = enddate - startdate + 1 (in days)

When no post-baseline assessments are available, the date of randomization/start of treatment will be used as enddate (duration = 1 day) when time is to be censored at last assessment, i.e. time to event variables can never be negative.

16.2.5.2 Date of last contact

The date of last contact will be derived for patients alive using the latest complete date among the following:

- Assessment dates (e.g., vital signs assessment, performance status assessment, efficacy assessment, laboratory, pharmacokinetics assessment)
- Medication dates including study medication and antineoplastic therapies administered after study treatment discontinuation
- Adverse events dates
- Last known date subject alive collected on the ‘Survival information’ eCRF
- Randomization date

16.2.5.3 Date of new anti-cancer therapy

The date of new anti-cancer therapy is the date of the first antineoplastic therapy (including medicine, radiotherapy and surgery) reported on the post-treatment antineoplastic therapy CRF or from other sources (e.g., HSCT CRF).

16.2.5.4 Incomplete assessment dates

All investigation dates (e.g., PET-CT scan) must be completed with day, month and year. If one or more investigation dates are incomplete but other investigation dates are available, this/these incomplete date(s) are not considered for calculation of the assessment date (and assessment date is calculated as outlined in [Section 16.2.4.5.3](#)). If all measurement dates have no day recorded, the 1st of the month is used.

If the month is not completed, for any of the investigations, the respective assessment will be considered to be at the date which is exactly between previous and following assessment. If a previous and following assessment is not available, this assessment will not be used for any calculation.

16.2.5.5 Incomplete dates for last contact or death

All dates must be completed with day, month and year. If the day is missing, the 15th of the month will be used for incomplete death dates or dates of last contact.

16.2.6 Appendices

Appendix A: Adaptation for use in maintenance/adjuvant settings

For study populations without measurable disease at baseline (e.g., maintenance), the event of interest is no longer progression but relapse, and the main endpoint is no longer progression-free survival but disease-free survival (see below).

Relapsed disease

Any of the following meets the definition of relapsed disease (RD):

- Any new nodal lesion > 15 mm in any axis (i.e. previously normal lymph node becoming >1.5 cm in any axis) on CT (or MRI) after baseline
- Any discrete extranodal lesion (including liver or spleen) reliably appearing on CT (or MRI) after baseline
- $\geq 50\%$ increase in long axis from baseline of any residual lymph node or mass. A residual lymph node or mass is defined as a previously lymphoma-involved lymph node or mass (>10 mm in short axis (without any upper limit)) that was PET negative at baseline and only reliably detected by baseline CT (or MRI). Note: If a residual lymph node or mass at baseline decreases in size during treatment and becomes normal (i.e. complete disappearance of extranodal mass or ≤ 10 mm in short axis and ≤ 15 mm long axis for nodal mass), then reappearance of an extranodal lesion at the same site or increase of the same nodal mass to > 15 mm in the long axis, will be considered RD and will be recorded as a new lesion.
- Any new bone marrow involvement

- Any new malignant effusion

Disease-free survival

Disease-free survival (DFS) is the time from date of randomization / start of treatment to the date of event defined as the first documented relapse of the disease or death due to any cause. If a patient has not had an event, DFS is censored at the date of the last adequate assessment. Similar censoring rules and reasons as the ones used for PFS can be applied.

16.3 Appendix 3: Tisagenlecleucel modified data reporting – Treatment and Follow Up Phase

Table 16-7 Data reporting: adverse events, concomitant medications, and laboratory values

	From ICF signature to safety follow-up visit	Only patients who receive tisagenlecleucel From safety follow-up visit ¹ until Month 60 or early discontinuation from study
AE and SAE	All, including all laboratory abnormalities deemed clinically significant by the investigator	<ul style="list-style-type: none"> Events leading to death Serious or opportunistic infections. Defined as bacterial, viral, fungal or parasitic infections that fulfill one of the following criteria: Lead to significant disability or hospitalization OR Need surgical or other intervention New incidence or exacerbation of a pre-existing neurologic disorder New incidence or exacerbation of a prior rheumatologic or other autoimmune disorder New incidence of other hematologic disorder New malignancy (T-cell & non T-cell), other than primary malignancy Any severe adverse event or condition the investigator believes may have a reasonable relationship to tisagenlecleucel or study procedures Positive RCL test result Vector insertion site sequencing result with a mono-or oligoclonality pattern or in a location near a known human oncogene Progressive multifocal leukoencephalopathy (PML) Hepatitis B reactivation
Concomitant medication	All	<ul style="list-style-type: none"> Treatment related to an AE or SAE from the above mentioned list Mutagenic agents (including cytotoxic drugs) Radiation & antineoplastic therapy (including SCT) Immunoglobulin therapy Immunosuppressive agents (including dose of steroids higher than physiologic replacement therapy doses of steroids (<12 mg/m2/day hydrocortisone or equivalent)) Investigational therapy
Laboratory data	All	<ul style="list-style-type: none"> Record all scheduled labs (per Visit Evaluation Schedule, Table 8-2) Record abnormal lab values that is in the opinion of the investigator related to the list of AEs and SAEs provided above.
1. Safety follow-up visit will take place 8 weeks after last treatment administration or prior to starting a new anti-cancer therapy, whichever occurs first.		

16.4 Appendix 4: Liver event and laboratory trigger definitions and follow-up requirements

Table 16-8 Liver event and laboratory trigger definitions

	Definition/ threshold
LIVER LABORATORY TRIGGERS	$3 \times \text{ULN ALT} / \text{AST} \leq 5 \times \text{ULN}$ $1.5 \times \text{ULN} < \text{TBL} \leq 2 \times \text{ULN}$
LIVER EVENTS	ALT or AST $> 5 \times \text{ULN}$ ALP $> 2 \times \text{ULN}$ (in the absence of known bone pathology) TBL $> 2 \times \text{ULN}$ (in the absence of known Gilbert syndrome) ALT or AST $> 3 \times \text{ULN}$ and INR > 1.5 Potential Hy's Law cases (defined as ALT or AST $> 3 \times \text{ULN}$ and TBL $> 2 \times \text{ULN}$ [mainly conjugated fraction] without notable increase in ALP to $> 2 \times \text{ULN}$) Any clinical event of jaundice (or equivalent term) ALT or AST $> 3 \times \text{ULN}$ accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia Any adverse event potentially indicative of a liver toxicity*
*These events cover the following: hepatic failure, fibrosis and cirrhosis, and other liver damage-related conditions; the non-infectious hepatitis; the benign, malignant and unspecified liver neoplasms TBL: total bilirubin; ULN: upper limit of normal	

Table 16-9 Follow up requirements for liver events and laboratory triggers

Criteria	Actions required	Follow-up monitoring
Potential Hy's Law case ^a	Discontinue the study treatment immediately (<i>if applicable</i>) Hospitalize, if clinically appropriate Establish causality Record the AE and contributing factors (e.g., concomitant medication, medical history, lab) in the appropriate CRF	ALT, AST, TBL, indirect and direct bilirubin, albumin, Alb, PT/INR, ALP and GGT, until resolution (frequency at investigator discretion)
ALT or AST		
> 8 × ULN	Discontinue the study treatment immediately (<i>if applicable</i>) Hospitalize if clinically appropriate Establish causality Record the AE and contributing factors (e.g., concomitant medication, medical history, lab) in the appropriate CRF	ALT, AST, TBL, indirect and direct bilirubin, albumin, Alb, PT/INR, ALP and GGT until resolution ^c (frequency at investigator discretion)
> 3 × ULN and INR > 1.5	Discontinue the study treatment immediately (<i>if applicable</i>) Hospitalize, if clinically appropriate Establish causality Record the AE and contributing factors (e.g., concomitant medication, medical history, lab) in the appropriate CRF	ALT, AST, TBL, indirect and direct bilirubin, albumin, Alb, PT/INR, ALP and GGT until resolution ^c (frequency at investigator discretion)
> 5 to ≤ 8 × ULN	Repeat LFT within 48 hours If elevation persists, continue follow-up monitoring If elevation persists for more than 2 weeks, discontinue the study drug (<i>if applicable</i>) Establish causality Record the AE and contributing factors (e.g., concomitant medication, medical history, lab) in the appropriate CRF	ALT, AST, TBL, indirect and direct bilirubin, albumin, Alb, PT/INR, ALP and GGT until resolution ^c (frequency at investigator discretion)
> 3 × ULN accompanied by symptoms ^b	Discontinue the study treatment immediately (<i>if applicable</i>) Hospitalize if clinically appropriate Establish causality Record the AE and contributing factors (e.g., concomitant medication, medical history, lab) in the appropriate CRF	ALT, AST, TBL, indirect and direct bilirubin, albumin, Alb, PT/INR, ALP and GGT until resolution ^c (frequency at investigator discretion)
> 3 to ≤ 5 × ULN (patient is asymptomatic)	Repeat LFT within the next week If elevation is confirmed, initiate close observation of the patient	Investigator discretion Monitor LFT within 1 to 4 weeks
ALP (isolated)		
> 2 × ULN (in the absence of known bone pathology)	Repeat LFT within 48 hours If elevation persists, establish causality Record the AE and contributing factors (e.g., concomitant medication, medical history, lab) in the appropriate CRF	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit

Criteria	Actions required	Follow-up monitoring
TBL (isolated)		
> 2 × ULN (in the absence of known Gilbert syndrome)	Repeat LFT within 48 hours If elevation persists, discontinue the study drug immediately (<i>if applicable</i>) Hospitalize if clinically appropriate Establish causality Record the AE and contributing factors (e.g., concomitant medication, medical history, lab) in the appropriate CRF	ALT, AST, TBL, indirect and direct bilirubin, albumin, Alb, PT/INR, ALP and GGT until resolution ^c (frequency at investigator discretion) Test for hemolysis (e.g., reticulocytes, haptoglobin, unconjugated [indirect] bilirubin)
> 1.5 to ≤ 2 × ULN (patient is asymptomatic)	Repeat LFT within the next week If elevation is confirmed, initiate close observation of the patient	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
Jaundice	Discontinue the study treatment immediately (<i>if applicable</i>) Hospitalize the patient Establish causality Record the AE and contributing factors (e.g., concomitant medication, medical history, lab) in the appropriate CRF	ALT, AST, TBL, indirect and direct bilirubin, albumin, Alb, PT/INR, ALP and GGT until resolution ^c (frequency at investigator discretion)
Any AE potentially indicative of a liver toxicity*	Consider study treatment interruption or discontinuation (<i>if applicable</i>) Hospitalization if clinically appropriate Establish causality Record the AE and contributing factors (e.g., concomitant medication, medical history, lab) in the appropriate CRF	Investigator discretion
^a Elevated ALT/AST > 3 × ULN and TBL > 2 × ULN but without notable increase in ALP to > 2 × ULN ^b (General) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia ^c Resolution is defined as an outcome of one of the following: (1) return to baseline values, (2) stable values at three subsequent monitoring visits at least 2 weeks apart, (3) remain at elevated level after a maximum of 6 months, (4) liver transplantation, and (5) death.		
Based on investigator's discretion investigation(s) for contributing factors for the liver event can include: serology tests, imaging and pathology assessments, hepatologist's consultancy; obtaining more detailed history of symptoms and prior or concurrent diseases, history of concomitant drug use, history of exposure to environmental chemical agents, exclusion of underlying liver disease.		

16.5 Appendix 5: Specific renal alert criteria and actions and event follow-up

Table 16-10 Specific renal alert criteria and actions

Renal Event	Actions
Confirmed serum creatinine increase 25 – 49%	Consider causes and possible interventions Follow up within 2-5 days
Serum creatinine increase $\geq 50\%$ + OR if <18 years old, eGFR ≤ 35 mL/min/1.73 m ²	Consider causes and possible interventions Repeat assessment within 24-48 hours if possible Consider drug interruption or discontinuation unless other causes are diagnosed and corrected Consider patient hospitalization and specialized treatment
New onset dipstick proteinuria $\geq 3+$ OR (Spot) urinary protein-creatinine ratio (PCR) ≥ 1 g/g (or mg/ mmol equivalent as converted by the measuring laboratory)	Consider causes and possible interventions Assess serum albumin & serum total protein Repeat assessment to confirm Consider drug interruption or discontinuation unless other causes are diagnosed and corrected
New onset hematuria $\geq 3+$ on urine dipstick	Assess & document <ul style="list-style-type: none"> • Repeat assessment to confirm • Distinguish hemoglobinuria from hematuria • Urine sediment microscopy • Assess serum creatinine • Exclude infection, trauma, bleeding from the distal urinary tract/bladder, menstruation • Consider bleeding disorder

*Corresponds to KDIGO criteria for Acute Kidney Injury

Table 16-11 Follow up of renal events

Assess, document and record in the appropriate CRF
<ul style="list-style-type: none"> • Urine dipstick and sediment microscopy evidence of DIN: crystals, red blood cells (dysmorphic/glomerular vs. non-dysmorphic/non-glomerular), white blood cells, tubular epithelial cells • Blood pressure and body weight • Serum creatinine, BUN, electrolytes (sodium, potassium, phosphate, calcium), bicarbonate and uric acid • Urine output
Review and record possible contributing factors to the renal event (co-medications, other co-morbid conditions) and additional diagnostic procedures (MRI etc.) in the CRF.
Monitor patient regularly (frequency at investigator's discretion) until:
<ul style="list-style-type: none"> • Event resolution: serum creatinine within 10% of baseline or PCR <1 g/g or albumin-creatinine ratio <300 mg/g)
or
<ul style="list-style-type: none"> • Event stabilization: serum creatinine level with $\pm 10\%$ variability over last 6 months or PCR stabilization at a new level with $\pm 50\%$ variability over last 6 months • Analysis of urine markers in samples collected over the course of the renal event

Novartis Research and Development

CTL019, tisagenlecleucel, Kymriah®

Clinical Trial Protocol CCTL019H2301

**Tisagenlecleucel versus standard of care in adult patients
with relapsed or refractory aggressive B-cell non-Hodgkin
lymphoma: A randomized, open label, phase III trial
(BELINDA)**

Document type: Amended Protocol Version

EUDRACT number: 2016-002966-29

Version number: 03 (Clean)

Development phase: III

Document status: Final

Release date: 08-Jan-2021

Property of Novartis

Confidential

May not be used, divulged, published, or otherwise disclosed
without the consent of Novartis

Clinical Trial Protocol Template Version 1.0 (01-Dec-2017)



Table of contents

Table of contents	2
List of tables	6
List of figures	8
List of abbreviations	9
Glossary of terms	15
Amendment 3 (08-Jan-2021)	17
Amendment 2 (18-Mar-2020)	19
Amendment 01-CN.01 (28-Oct-2019)	24
Amendment 1 (22-Feb-2019)	26
Protocol summary	37
1 Introduction	44
1.1 Background	44
1.1.1 Overview of disease pathogenesis, epidemiology and current treatment	44
1.1.2 Historical experience with viral gene therapies	48
1.1.3 Overview of tisagenlecleucel	49
1.2 Purpose	52
2 Objectives and endpoints	53
3 Study design	56
4 Rationale	58
4.1 Rationale for study design	58
4.1.1 Rationale for lymphodepletion	59
4.2 Rationale for dose/regimen and duration of treatment	60
4.3 Rationale for choice of comparator drugs	60
4.4 Purpose and timing of interim analyses	61
4.5 Risks and benefits	61
4.5.1 Identified safety risks with the use of tisagenlecleucel	62
4.5.2 Potential safety risks	70
4.5.3 Other risks	73
5 Population	74
5.1 Inclusion criteria	74
5.2 Exclusion criteria	76
6 Treatment	78
6.1 Study treatment	78
6.1.1 Investigational and control drugs	78
6.1.2 Tisagenlecleucel pre-infusion evaluation	80

6.1.3	Additional safety procedures prior to tisagenlecleucel infusion	81
6.1.4	Additional study treatments	82
6.1.5	Treatment arms.....	84
6.1.6	Treatment duration	84
6.1.7	Dosing regimen	85
6.2	Other treatment(s).....	86
6.2.1	Concomitant therapy	86
6.2.2	Prohibited concomitant medication and non-drug therapy	86
6.3	Participant numbering, treatment assignment, randomization	87
6.3.1	Participant numbering	87
6.3.2	Treatment assignment, randomization	88
6.4	Treatment blinding.....	88
6.5	Dose modification.....	89
6.5.1	Follow-up for toxicities.....	89
6.6	Additional treatment guidance.....	90
6.6.1	Treatment compliance.....	90
6.6.2	Recommended treatment for adverse events.....	91
6.6.3	Emergency breaking of assigned treatment code.....	95
6.7	Preparation and dispensation	96
6.7.1	Handling of study treatment and additional treatment.....	96
7	Informed consent procedures	97
8	Visit schedule and assessments	97
8.1	Screening	133
8.1.1	Eligibility screening	135
8.1.2	Information to be collected on screening failures	135
8.2	Participant demographics/other baseline characteristics	135
8.3	Efficacy.....	136
8.3.1	Transmission of efficacy data to BIRC	140
8.3.2	Non-expedited review - timepoints without locally determined progression or stable disease	140
8.3.3	Expedited review - timepoints with locally determined progression or stable disease.....	141
8.4	Safety	142
8.4.1	Laboratory evaluations.....	143
8.4.2	Electrocardiogram (ECG)	144
8.4.3	Pregnancy and fertility	146
8.4.4	Spirometry.....	146

8.4.5	Other safety evaluations	146
8.4.6	Appropriateness of safety measurements	146
8.5	Additional assessments	146
8.5.1	Patient reported outcomes (PRO).....	146
8.5.2	Pharmacokinetics/ Cellular Kinetics	149
8.5.3	Biomarkers	160
8.5.4	Imaging	167
8.5.5	Survival follow-up	167
8.5.6	Other assessments	167
9	Study discontinuation and completion	167
9.1	Discontinuation.....	167
9.1.1	Discontinuation of study treatment	167
9.1.2	Criteria for premature patient discontinuation from the study.....	168
9.1.3	Withdrawal of informed consent.....	169
9.1.4	Lost to follow-up.....	170
9.1.5	Early study termination by the sponsor.....	170
9.1.6	Criteria for stopping or pausing the study.....	170
9.2	Study completion and post-study treatment	171
10	Safety monitoring and reporting.....	172
10.1	Definition of adverse events and reporting requirements.....	172
10.1.1	Adverse events	172
10.1.2	Serious adverse events	174
10.1.3	SAE reporting.....	175
10.1.4	Adverse events of special reporting requirements	176
10.1.5	Pregnancy reporting	176
10.1.6	Reporting of study treatment errors	177
10.2	Additional safety monitoring.....	177
10.2.1	Liver safety monitoring.....	177
10.2.2	Renal safety monitoring	178
10.2.3	Data Monitoring Committee	178
10.2.4	Steering committee.....	179
10.2.5	Blinded independent review committee (BIRC).....	179
10.2.6	Follow up of secondary malignancy	179
11	Data collection and database management.....	179
11.1	Data collection	179
11.2	Database management and quality control	180

11.3	Site monitoring	180
12	Data analysis and statistical methods	181
12.1	Analysis sets	181
12.1.1	Screened Set	182
12.1.2	Infused Set.....	182
12.1.3	Full Analysis Set	182
12.1.4	Safety Set	182
12.1.5	Per-Protocol Set	182
12.1.6	Cellular Kinetic Analysis Set.....	182
12.2	Participant demographics and other baseline characteristics.....	182
12.3	Treatments	183
12.4	Analysis of the primary endpoint	183
12.4.1	Definition of primary endpoint	183
12.4.2	Statistical model, hypothesis, and method of analysis.....	184
12.4.3	Handling of missing values/censoring/discontinuations.....	184
12.4.4	Sensitivity and supportive analyses	185
12.5	Analysis of secondary endpoints	186
12.5.1	Efficacy and/or pharmacodynamic endpoints.....	187
12.5.2	Safety endpoints.....	188
12.5.3	Patient reported outcomes	192
12.5.4	Cellular kinetics	193
12.5.5	Biomarkers	194
12.5.6	Efficacy in sub-populations.....	196
12.6	Analysis of exploratory endpoints.....	196
12.6.1	Efficacy and safety after crossover	196
12.6.2	Healthcare resource utilization.....	196
12.7	Interim analyses	196
12.8	Sample size calculation.....	197
12.8.1	Primary endpoints	197
13	Ethical considerations and administrative procedures	197
13.1	Regulatory and ethical compliance.....	197
13.2	Responsibilities of the investigator and IRB/IEC.....	198
13.3	Publication of study protocol and results.....	198
13.4	Quality control and quality assurance.....	198
14	Protocol adherence	198
14.1	Protocol Amendments	199

15	References (available upon request).....	200
16	Appendices	209
16.1	Appendix 1: Assessment algorithms for hepatitis B and C status at screening..	209
16.2	Appendix 2: Guidelines for efficacy evaluation in non-Hodgkin-Lymphoma studies	210
16.2.1	Introduction	210
16.2.2	Methodologies	210
16.2.3	Definitions.....	211
16.2.4	Efficacy assessments	213
16.2.5	Data handling and programming conventions	225
16.2.6	Appendices	226
16.3	Appendix 3: Modified data reporting by study period	228
16.4	Appendix 4: Liver event and laboratory trigger definitions and follow-up requirements	229
16.5	Appendix 5: Specific renal alert criteria and actions and event follow-up.....	232

List of tables

Table 1-1	Phase III trials in relapsed/refractory DLBCL	46
Table 2-1	Objectives and related endpoints	53
Table 4-1	Clinical signs and symptoms associated with CRS.....	63
Table 4-2	Cytokine Release Syndrome Grading	63
Table 4-3	Immune effector Cell-Associated Neurotoxicity Syndrome (ICANS) Grading	65
Table 4-4	Immune effector Cell-associated Encephalopathy (ICE) score	67
Table 6-1	Defined risk factors and risk groups of International Prognostic Index (IPI)	88
Table 6-2	CRS management.....	92
Table 6-3	Definition of high dose vasopressor use	92
Table 8-1	Visit evaluation schedule pre-screening to randomization	99
Table 8-2	Visit evaluation schedule for Arm A (patients randomized to tisagenlecleucel treatment strategy)	102
Table 8-3	Visit evaluation schedule for Arm B (patients randomized to SOC treatment strategy).....	115
Table 8-4	Visit evaluation schedule for patients who cross over from Arm B (SOC) to Arm A (tisagenlecleucel).....	121
Table 8-5	Imaging or disease assessment collection plan	140
Table 8-6	ECOG performance status grade.....	142

Table 8-7	Physical assessments	143
Table 8-8	Laboratory assessments – Central Assessments	144
Table 8-9	Laboratory Assessments – Local Assessments	144
Table 8-10	Non compartmental cellular kinetics parameters	150
Table 8-11	Validated analytical methods and limit of quantification associated with the cellular kinetic analytes and immunogenicity assessments ..	151
Table 8-12	Tisagenlecleucel cellular kinetics by qPCR in peripheral blood collection log for patients in screening to randomization, Arm A, and in patients that cross over from Arm B to Arm A.	153
Table 8-13	Tisagenlecleucel cellular kinetics by flow cytometry in peripheral blood collection log for patients in screening to randomization, and Arm A, and in patients that cross over from Arm B to Arm A.	155
Table 8-14	Tisagenlecleucel cellular kinetics by q-PCR in bone marrow aspirate collection log for patients in screening to randomization, Arm A, and for patients that cross over from Arm B to Arm A.	156
Table 8-15	Tisagenlecleucel cellular kinetics by q-PCR in CSF	156
Table 8-16	Humoral Immunogenicity serum sample collection for patients in screening to randomization, and Arm A, and in patients that cross over from Arm B to Arm A.....	157
Table 8-17	Cellular Immunogenicity peripheral blood sample collection log for patients in screening to randomization, and Arm A, and in patients that cross over from Arm B to Arm A.	158
Table 8-18	Tisagenlecleucel cellular kinetics by qPCR in tocilizumab treated patients during CRS in Arm A and in patients that crossover from Arm B to Arm A	159
Table 8-19	Biomarker sample collection- peripheral blood for serum cytokine and soluble marker analyses.....	163
Table 8-20	Biomarker sample collection – B cell levels (peripheral blood).....	164
Table 8-21	Biomarker sample collection – immunophenotyping, gene expression profiling, (peripheral blood) and ctDNA plasma for MRD and tumor clonal analysis by Ig deep sequencing.....	165
Table 8-22	Sample collection – biomarker exploratory analysis and CAR expression on tumor biopsy	166
Table 10-1	Guidance for capturing the study treatment errors including misuse/abuse	177
Table 16-1	Five Point Scale (5PS)	211
Table 16-2	Radiological response assessment.....	216
Table 16-3	Overall disease response	219
Table 16-4	Censoring reasons	223
Table 16-5	Options for event dates used in PFS, EFS, TTP, DOR.....	224

Table 16-6	Data reporting adverse events, concomitant medications, and laboratory values	228
Table 16-7	Liver event and laboratory trigger definitions	229
Table 16-8	Follow up requirements for liver events and laboratory triggers	229
Table 16-9	Specific renal alert criteria and actions	232
Table 16-10	Follow up of renal events	232

List of figures

Figure 1-1	Tisagenlecleucel chimeric antigen receptor design.....	50
Figure 3-1	Global Study design*	57



List of abbreviations

5PS	5 point scale
AAIPI	Age-adjusted international prognostic index
ABC	Activated B-cell
AE	Adverse event
AESI	Adverse events of special interest
ALC	Absolute lymphocyte count
ALK	Anaplastic Lymphoma Kinase
ALL	Acute Lymphoblastic Leukemia
ALP	Alkaline phosphate
ALS	Amyotrophic lateral sclerosis
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
aPTT	Activated partial thromboplastin time
ASH	American Society of Hematology
AST	Aspartate aminotransferase
ASTCT	American Society of Transplantation and Cellular Therapy
ATC	Anatomical therapeutic chemical
AUC	Area under the curve
AV block	Atrioventricular block
B-ALL	B-cell acute lymphoblastic leukemia
Bcl-2	B-cell lymphoma 2
BEAM	Carmustine, Etoposide, Cytarabine, Melphalan
BIRC	Blinded Independent Review Committee
BM	Bone marrow
BOR	Best overall response
BUN	Blood Urea Nitrogen
CABG	Coronary artery bypass graft
CAR	Chimeric antigen receptor
CCG	CRF Completion Guidelines
CD19 CART	CD 19 redirected chimeric antigen receptor T cell
CDS	Core data sheet
CFR	Code of Federal Regulations
CHOP	Cyclophosphamide, doxorubicin, vincristine, prednisone
CI	Confidence Interval
CK	Cellular kinetics
CKAS	Cellular kinetic analysis set
C _{last}	Concentration last
CLL	Chronic Lymphocytic Leukemia
C _{max}	Maximum concentration
CMO&PS	Chief Medical Office and Patient Safety
CMR	Complete metabolic response
CMV	Cytomegalovirus
c-myc	c-myc proto-oncogene
CNS	Central Nervous System
CORAL	Collaborative Trial in Relapsed Aggressive Lymphoma
CR	Complete Response

CRF	Case Report/Record Form; the term CRF can be applied to either EDC or Paper
CRO	Contract research organization
CRP	C-Reactive Protein
CRS	Cytokine release syndrome
CSF	Cerebral spinal fluid
CSP	Clinical study protocol
CSR	Clinical study report
CT	Computed tomography
CTC	Common toxicity criteria
CTCAE	Common terminology criteria for adverse events
CV%	Coefficient of Variation (%)
DFS	Disease free survival
DHAP	Dexamethasone, high dose, cytarabine (Ara-C, cisplatin (platinum))
DILI	Drug induced liver injury
DLBCL	Diffuse large B-cell lymphoma
DLCO	Diffusing capacity carbon monoxide
DMC	Data monitoring committee
DNA	Deoxyribonucleic acid
DOR	Duration of Response
DRESS	Drug reaction with eosinophilia and systemic symptoms
EBV	Epstein-Barr virus
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture
EDTA	Ethylenediaminetetraacetic acid
EEG	Electroencephalography
EFS	Event free survival
eGFR	Estimated Glomerular Filtration Rate
ePRO	Electronic patient reported outcome
EQ-VAS	EuroQoL visual analogue scale
EQ-5D	EuroQoL 5 dimensions
EMA	European Medicines Agency
EOS	End of study
ESMO	European Society for Medical Oncology
EU	European Union
EWB	Emotional Well-Being
FACT-G	Functional assessment of cancer therapy general
FACT-Lym	Functional assessment of cancer therapy lymphoma
FACT-LymS	Functional assessment of cancer therapy lymphoma subscale
FACT-TOI	Functional assessment of cancer therapy total outcome index
FACT-TS	Functional assessment of cancer therapy total score
FAS	Full analysis set
FDA	Food & Drug Administration
FDG	Fluorodeoxyglucose
FEV1	Forced expiratory volume in one second

FH	Fleming-Harrington
FISH	Fluorescence in situ hybridization
FL	Follicular lymphoma
FL3B	Follicular lymphoma grade 3B
FNA	Fine needle aspirate
FPFV	First Patient First Visit
FWB	Functional well-being
GBS	Guillain-Barre syndrome
GCB	Germinal center B-cell
GCP	Good Clinical Practice
G-CSF	Granulocyte colony stimulating factor
GDP	Gemcitabine, dexamethasone, cisplatin
GemOx	Gemcitabine, oxaliplatin
GEP	Gene expression profiling
GGT	Gamma glutamyl transferase
GI	Gastrointestinal
GM-CSF	Granulocyte macrophage-colony stimulating factor
GVHD	Graft versus host disease
HBcAb	Hepatitis B core antibody
HBsAb	Hepatitis B surface antibody
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HDCT	High dose chemotherapy
HIV	Human immunodeficiency virus
HL	Hodgkin lymphoma
HLH	Hemophagocytic lymphohistiocytosis
HR	Hazard ratio
HR	Heart rate
HRQoL	Health related quality of life
HSC	Hematopoietic stem cell
HSCT	Hematopoietic stem cell transplantation (refers to both allogenic SCT and autologous SCT)
HSV	Herpes simplex virus
i.v.	Intravenous(ly)
IB	Investigator's brochure
ICE	Ifosfamide, carboplatin, etoposide
ICF	Informed consent form
ICH	International Council on Harmonization
ICU	Intensive care unit
IDO	Indoleamine 2,3-dioxygenase
IEC	Independent ethics committee
IFN-g	Interferon gamma
Ig	Immunoglobulin
IHC	Immunohistochemistry
IL	Interleukin
IMP	Investigational medicinal product
IN	Investigator notification

INR	International normalized ratio
IPI	International prognostic index
IRB	Institutional Review Board
IRT	Interactive response technology
IT	Intrathecal
ITP	Autoimmune thrombocytopenia/thrombocytopenic purpura
ITT	Intent to treat
IUD	Intrauterine device
IUS	Intrauterine System
IWRS	Interactive web response system
LD	Lymphodepletion
LDH	Lactate dehydrogenase
LDi	Longest diameter
LFT	Liver function tests
LISA	Lentivirus insertion site analysis
LLOQ	Lower limit of quantification
LPLV	Last Patient Last Visit
LSS	Lymphoma specific survival
LTFU	Long Term Follow Up
LTR	Long terminal repeat
LVEF	Left ventricular ejection fraction
MAS	Macrophage activation syndrome
MCHC	Mean corpuscular hemoglobin concentration
MCS	Mental component summary
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MHC	Major histocompatibility complex
MMc	Maternal microchimerism
mPFS	Median progression free survival
MRA	Magnetic resonance angiography
MRD	Minimum residual disease
MRI	Magnetic resonance imaging
MUGA	Multigated acquisition
NCCN	National Comprehensive Cancer Network
NCIC-CTG	National Cancer Institute of Canada Clinical Trials Group
NE	Norepinephrine equivalent
NGS	Next generation sequencing
NHL	Non-Hodgkin's Lymphoma
NK	Natural killer cell
NMPA	National Medicinal Products Administration
NMR	No metabolic response
NOS	Not otherwise specified
NYHA	New York Heart Association
ORR	Overall response rate
OS	Overall survival
PB	Peripheral blood
PBMC	Peripheral blood mononuclear cells

PCR	Polymerase Chain Reaction
PCS	Physical component summary
PD	Progressive disease or Pharmacodynamics
PD1	Programmed cell death 1
PDL1	Programmed death ligand 1
PET	Positron emission tomography
PFS	Progression free survival
PK	Pharmacokinetics
PMBCL	Primary mediastinal large B-cell lymphoma
PMD	Progressive metabolic disease
PML	Progressive multifocal leukoencephalopathy
PMR	Partial metabolic response
PPD	Perpendicular diameter
PPS	Per-protocol set
PR	Partial response
PRO	Patient reported outcome
PT	Preferred term or Prothrombin time
PTLD	Post-transplant lymphoproliferative disorders
PWB	Physical Well-Being
q12hr	Every 12 hours
QA	Quality Assurance
QMS	Quality Management System
qPCR	Quantitative polymerase chain reaction
QTcF	QT interval correction formula
R	Rituximab
r/r	Relapsed or refractory
RAP	Reporting and analysis plan
RCL	Replication competent lentivirus
RD	Relapsed disease
RNA	Ribonucleic acid
RoW	Rest of World
SAE	Serious Adverse Event
SAP	Statistical analysis plan
SC	Steering committee
scFv	Single chain variable fragment
SCT	Stem cell transplantation
SD	Stable Disease
SDi	Shortest diameter
SF-36	Short Form 36 health survey
SGOT	Serum glutamic-oxaloacetic transaminase
SGPT	Serum glutamic-pyruvic transaminase
SNP	Single nucleotide polymorphism
SOC	System organ class or Standard of care
SPD	Sum of the product of the diameters
SUSAR	Suspected unexpected serious adverse reactions
SUV	Standardized uptake value
SWB	Social well being

T _{1/2}	Time to half life
TBIL	Total bilirubin
TCR	T cell receptor
TdP	Torsades de pointes
T/HRBCL	T-cell/Histiocyte-rich B-cell Lymphoma
T _{last}	Timepoint of last measurable concentration
TLS	Tumor lysis syndrome
T _{max}	Time to peak concentration
TNF	Tumor necrosis factor
TPR	Timepoint response
TTP	Time to progression
TTCR	Time to complete response
TTR	Time to response
ULN	Upper limit of normal
UNK	Unknown
US	Ultrasound
USPI	United States Prescribing Information
V _H	Heavy Chain Variable Domain
V _L	Light Chain Variable Domain
VSV	Vesicular Stomatitis Virus
VSV-G	Vesicular Stomatitis Virus/Glycoprotein
WBC	White blood cells
WHO	World Health Organization
WOCBP	Women of child bearing potential

Glossary of terms

Assessment	A procedure used to generate data required by the study
Screening (Baseline) Efficacy Assessment	The assessment is done within 4 weeks of randomization. If multiple assessments are performed then the one closest temporally to randomization will serve as baseline assessment.
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study subject or patient
(Optional) Bridging Therapy	Rituximab based therapy given prior to tisagenlecleucel infusion
Cohort	A specific group of subjects fulfilling certain criteria and generally treated at the same time
Dose level	The dose of drug given to the patient (total daily or weekly etc.)
Investigational drug	The study treatment whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with "investigational new drug."
Investigational treatment	Drug whose properties are being tested in the study as well as their associated placebo and active treatment controls (when applicable). This also includes approved drugs used outside of their indication/approved dosage, or that are tested in a fixed combination. Investigational treatment generally does not include other study treatments administered as concomitant background therapy required or allowed by the protocol when used within approved indication/dosage
Period	A subdivision of the study timeline; divides stages into smaller functional segments such as screening, baseline, titration, washout, etc.
Personal Data	Subject information collected by the Investigator that is transferred to Novartis for the purpose of the clinical trial. This data includes subject identifier information, study information and biological samples.
Premature patient withdrawal	Point/time when the patient exits from the study prior to the planned completion of all study treatment administration and/or assessments; at this time all study treatment administration is discontinued and no further assessments are planned, unless the patient will be followed for progression and/or survival
RAP	Report and analysis plan is a regulatory document which provides evidence of preplanned analyses
Randomization	Point or time when patients have met all clinical eligibility and are assigned to Arm A (optional bridging chemo + lymphodepleting chemotherapy + tisagenlecleucel) or Arm B (SOC)
Stage related to study timeline	A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, randomization, completion of treatment, etc.
Stop study participation	Point/time at which the patient came in for a final evaluation visit or when study treatment was discontinued whichever is later
Study treatment	Includes any drug or combination of drugs in any study arm administered to the patient (subject) as part of the required study procedures, including lymphodepleting chemotherapy. In specific examples, it is important to judge investigational treatment component relationship relative to a study treatment combination; study treatment in this case refers to the investigational and non-investigational treatments in combination.
Study treatment discontinuation	Point/time when a patient permanently stops taking study treatment for any reason
Subject Number	A number assigned to each subject upon signing the informed consent. This number is the definitive, unique identifier for the subject and should be used to identify the subject throughout the study for all data collected, sample labels, etc.
Variable	A measured value or assessed response that is determined from specific assessments and used in data analysis to evaluate the drug being tested in the study

Withdrawal of study consent	Withdrawal of consent from the study occurs only when a subject does not want to participate in the study any longer, and does not allow any further collection of personal data
-----------------------------	--



Amendment 3 (08-Jan-2021)

Amendment rationale

As of 08-Jan-2021, 298 participants out of 318 planned participants have been randomized on the study.

The main purpose of this amendment is to introduce the option to continue recruitment in a China extension cohort, following completion of enrollment in the main cohort (target of 318 participants) in order to support registration of Kymriah in the respective indication in China. The China extension cohort has no impact on the planned primary analysis of the global study, in particular the sample size and number of EFS events required for the primary analysis remain unchanged. Any Chinese patients recruited in the global study will be included in the primary analysis of the global study.

Once recruitment in the global study is completed, recruitment in the China extension cohort will begin. At least 36 participants from China mainland are planned to be randomized in the study (in the global study or/and in the China Extension cohort). The number of participants to be enrolled in the China Extension cohort will depend on the number of Chinese participants enrolled in the main cohort of this global study. The recruitment in the China Extension cohort will not initiate if the number of participants enrolled in the global study main cohort is sufficient to meet regulatory requirements for registration in China.

Data from all participants from China mainland will be pooled and analyzed separately for inclusion in the registration dossier to the Chinese regulatory authority. Therefore, data from participants from China mainland randomized prior to the completion of global enrollment will be part of both the main cohort global analysis and the China extension cohort analysis.

The primary analysis of the participants from China mainland will be conducted once 36 patients from China mainland have been randomized and approximately 18 EFS events have been documented by the BIRC in Chinese mainland participants.

Additionally, with this amendment, an evaluation of the study in the context of the COVID-19 pandemic was assessed; the benefit/risk of the study remains favorable. Adequate strategies were put in place at site levels to mitigate potential disruptions due to the COVID-19 pandemic.

Other minor changes or protocol clarifications not directly related to the China extension are included in this amendment.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underline for insertions. Significant changes are listed below.

The following changes are made due to the introduction of the China extension cohort:

- Section 3 was updated to add the China extension cohort to allow randomization of at least 36 participants from China mainland following achievement of global study main cohort recruitment target.



- Figure 3-1 footnote was added to clarify that the extension cohort will follow the same study design.
- Section 5 added language regarding the China extension cohort.
- Table 6-1 sentence was added to clarify China extension cohort to be stratified by remission duration and IPI. The region stratum would not be applicable for this cohort.
- Section 10.1.4 Adverse events of special reporting requirements: sentence added to clarify the initial SAE report will follow local regulations/HA requirements.
- Section 12, 12.4.2, and 12.8.1 are updated to include discussion of China extension cohort, with respect to primary analysis of EFS, primary endpoint, and sample size calculation.

Minor changes related to protocol clarifications are listed below:

- Section 3, Table 6-1, and Section 8.1.1 clarify that IPI should be evaluated based on central lab values for LDH at study entry.
- Section 4.5.2.2 added updated language on RCL risk.
- Section 5.1 Inclusion criteria 8c formatting corrected.
- Section 5.2 Exclusion criteria 10f ii formatting corrected.
- Section 6.1.1 and 6.1.2 language has been added that palliative radiotherapy is allowed
- Section 6.3.1 Participant numbering section updated to allow re-screening with a different participant number.
- Section 6.5 added special consideration for use of chemotherapy not specified by the protocol.
- Section 6.6.2.9, Section 8.4.5, and Section 12.5.2 added text about the storage of RCL samples after month 12 when prior testing is negative.
- Table 6-1 provides clarification on extranodal involvement.
- Section 8.1 Screening updated to allow for re-screening upon discussion with the medical monitor. Patient re-screening may only be performed once per patient.
- Section 10.2.6 was updated for secondary malignancy follow-up.

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation.



Amendment 2 (18-Mar-2020)

Amendment rationale

As of 25-Feb-2020, 107 participants out of 318 planned participants have been randomized on the study.

The main purpose of this amendment is:

1. To incorporate time to response as a secondary endpoint on the study, as this is an important aspect to describe the efficacy outcome for both study arms.
2. To incorporate feedback from the data monitoring committee regarding the pre-infusion evaluation criteria in [Section 6.1.2](#) to clarify the previously written criteria. This was important to guide investigators to a more thorough review of pre-infusion criteria due to patient safety findings when rapidly progressing patients have been infused. These clarifications have already been implemented with a dear investigator letter, and are now being adopted into the protocol.

In addition, other changes and clarifications were made after consultation with the study steering committee to clarify certain eligibility criteria and some aspects of study conduct. These changes were aimed to improve study recruitment and compliance, while still maintaining safe and effective research in the desired study population with unmet medical need.

Key changes include:

- Changes were made to the inclusion criteria to allow patients who have suboptimal response (not CR) to first line therapy. This is consistent with NCCN guidelines and this population would be expected to have a similar prognosis to the current population ([NCCN v15, 2019](#)).
- Changes were made to safety reporting criteria in [Section 10.1.3](#) due to inconsistency with the modified data reporting in [Section 16.3 Appendix 3](#).
- Rituximab washout periods were removed as there is no clear scientific evidence of rituximab inhibiting the mechanism of action of tisagenlecleucel, and the long half life of rituximab makes it impossible to sufficiently remove this drug from the body with any reasonable amount of washout. The removal of this washout improves patient safety and removes the burden of modifying bridging and SOC chemotherapy regimens before infusion.
- Additional changes were made based on feedback received from investigators and to clarify questions and address obstacles to protocol compliance observed to date.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underline for insertions. Significant changes are listed below:

- Protocol summary section updated to align with content of protocol body.



- Table 2-1 was updated to include a secondary objective/endpoint for time to response (TTR).
- Section 3 Study Design updated:
 - Arm A paragraph sentence was deleted: “In order to comply with the 4 week washout period for rituximab therapy prior to tisagenlecleucel infusion (see Section 6.2.2), rituximab may need to be omitted from the last cycle of bridging chemotherapy.”
 - Arm B sentence clarified: “... patients with PR FDG+ disease, SD or PD per local assessment may request manufacturing
- Table 4-1 Neurologic was deleted from the clinical signs and symptoms associated with CRS.
- Section 4.5.2.4 sentence deleted to align with IB, “The use of tocilizumab a monoclonal antibody against the IL-6 receptor, can exacerbate demyelinating disease, and therefore its use is to be used with precaution in such conditions [Actemra® USPI].”
- Section 4.5.3.1 clarified that qPCR tests are available upon request
- Section 5 sentence added for clarification “Central lab must be used to confirm eligibility of all lab parameters listed in Section 5.1 and Section 5.2.”
- Section 5.1 Inclusion criteria updated:
 - Inclusion Criteria #3 was updated to include “PR” after at least 6 cycles of first line treatment, a new biopsy must be submitted.
 - Inclusion Criteria #4 was updated to include patients who received other anti-CD20 antibody besides rituximab
 - Inclusion Criteria #6 was updated to ensure patients with active disease are included in the trial.
 - Inclusion Criteria #8c was updated to align with reference manual
- Section 5.2 Exclusion criteria was updated:
 - Exclusion criteria #3 updated to note that treatment for second line “systemic” lymphoma is excluded. Updated sentence to include local irradiation is permitted.
 - Exclusion criteria #4 deleted parenthetical example as asymptomatic disease is not necessarily a sign of no active CNS involvement
- Section 6.1.1 Investigational and control drugs updated:
 - Investigational Drug section clarified that “Patients that crossover to arm A after failing treatment with SOC chemotherapy may use any type of bridging therapy at the investigator’s discretion and are not restricted to the four bridging therapies specified in the protocol Section 3 and Section 6.1.1.” (similar change made in Section 6.1.4 and 6.1.7)
- Section 6.1.2 Pre-infusion evaluation updated based on DMC recommendation:
 - Added sentence: “In case of any doubt on fulfillment of pre-infusion evaluation criteria, the medical monitor may be contacted. The investigator will be required to sign the tisagenlecleucel pre-infusion checklist stating fulfillment of pre-infusion criteria within 24 hours prior to tisagenlecleucel infusion. Criteria must continue to be monitored after the form is signed until the time of infusion in case of any worsening of status which would preclude tisagenlecleucel infusion.”

- Evaluation #1 updated to include detail on rising LDH values and ECOG performance status changes
- Evaluation #4 updated note to specify the tests “HBV, HCV, and HIV”
- Section 6.2.1 clarified investigator discretion in use of drugs with known risk of QTc prolongation and/or “Torsades de Pointes”
- Section 6.2.2 Prohibited concomitant medication and non-drug therapy:
 - Medication restrictions section updated #3 to “Antibody use except anti-CD20 therapy (e.g., rituximab) should not be used within 4 weeks prior to tisagenlecleucel infusion.”
- Section 6.3.2 clarified refractory and relapse definition for stratification
- Section 6.6.2.1 updated tocilizumab availability to align with latest RMP
- Section 8 Visit Schedule and Assessments was updated to provide more clarity on study phasing and survival follow-up details
- Table 8-1 Visit evaluation schedule pre-screening to randomization updated:
 - At screening Spirometry, ECHO/MRA/MUGA, ECG assessments are (allowed up to 4 weeks prior to randomization)
 - Footnote 4 added
- Table 8-2 Visit evaluation schedule for Arm A (patients randomized to tisagenlecleucel treatment strategy) updated:
 - Pre-infusion criteria evaluation was updated to clarify the requirement to complete mandatory signed form within 24 hours prior to tisagenlecleucel infusion
 - IL6R assessment deleted as this test will not be performed
 - Footnote 3 sentence addition
- Table 8-3 Visit evaluation schedule for Arm B (patients randomized to SOC treatment strategy) updated:
 - Updated visit HSCT Day to HSCT Day 1
 - Renamed “End of Treatment and Follow-up” to “End of Treatment and Primary Follow-up”
 - Footnote 3 sentence addition
- Table 8-4 visit evaluation schedule for patients who cross over from Arm B (SOC) to Arm A (tisagenlecleucel) updated:
 - Changed Visit Safety and Efficacy Follow-up visits to be timed based on crossover visit date”
 - Pre-infusion criteria evaluation was updated to clarify the requirement to complete mandatory signed form within 24 hours prior to tisagenlecleucel infusion
 - IL6R assessment deleted
 - Footnote 3 sentence addition
 - Footnote 7 corrected as BIRC confirmed imaging is not done after crossover
- Section 8.1 Screening updated:

- Deleted Central Flow Cytometry, Serum Immunoglobulin levels and Viral Serology as assessments that do not need to be repeated if performed in the context of leukapheresis procedure or if performed as part of the clinical routine within 4 weeks of randomization.
- Added Cardiac and Lung function evaluation.
- Leukapheresis section specific treatment medications updated to refer to [Investigator Leukapheresis, Cryopreservation, and Scheduling Manual]”
- Sentence updated to allow rescreening upon consultation and agreement with the medical monitor.
- Section 8.1.1 added sentence: Novartis will supply a stratification form which must be signed and returned prior to randomization to ensure adequate documentation of stratification factors.
- Section 8.3 Efficacy updated to:
 - “Efficacy assessment should be also performed before initiation of new anticancer therapy in all patients if there has not already been an adequate imaging assessment demonstrating BIRC-confirmed SD/PD.”
 - Added sentence: “The crossover visit should also mark the end of the treatment and primary follow-up visit for patients in Arm B.”
 - Disease characterization at baseline and evaluation of efficacy point 4 updated to CNS Brain Imaging (CT/MRI and/or diagnostic lumbar puncture with CSF cytology (mandatory at screening and at discretion of the Investigator to evaluate CNS disease thereafter)
 - Table 8-5 updated Tumor biopsy (FFPE) treatment assessment reference to Table 8-22 “for mandatory” exploratory collections.
 - Imaging assessments section sentence rephrased for clarification of CNS disease assessment
 - Sentence “The status of primary malignancy based on clinical routine assessments will be recorded for patients with ongoing response during follow up. The CD19 status at time of relapse should be recorded.” deleted from this section and moved to Section 8.5.3 with new wording
- Table 8-8 updated to include RCL by VSV-g q-PCR
- Section 8.4.2, 8.4.2.1 and 8.4.4 updated to allow ECG, cardiac imaging and spirometry already completed during the regular care of the participant within 4 weeks prior to randomization; including before signing the main study ICF can be considered as the screening assessments for this study.
- Section 8.5.1 Patient reported outcomes (PRO) clarified that “The responses stored electronically in the database will be considered the source file.” Deleted the need to print a copy of the PRO questionnaires.
- Table 8-16 and Table 8-17 footnote updated
- Table 8-18 updated

- Section 8.5.3 Biomarkers updated to include sentence on the analysis of tumor biopsy section indicating “For patients who are PR after 6 cycles of first line therapy, archival tumor biopsy is not allowed.”
- Sections 9.1.1, 9.1.2, 9.1.3 clarified study phasing and visits to complete upon discontinuation from each phase of the trial
- Section 9.2 was reordered to clarify the study completion and post treatment study phasing
- Section 10.1.3 SAE reporting was modified because it was not consistent with modified safety reporting in Section 16.3
- Section 10.1.5 Pregnancy reporting sentence added according to updated global protocol template
- Section 12.1.5 Updated protocol deviation to include “PR”.
- Section 12.5 Updated to include “time to response (TTR)
- Section 12.5.1.1 Overall response rate (ORR) sentence added: “A descriptive summary of patients’ disease response status at the Week 6 assessment will also be provided.” This is to characterize disease status after bridging therapy.
- Section 12.5.1.3 Time to response (TTR) entire section was added to describe the Time to overall disease response.

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation.



Summary of previous amendments

Amendment 01-CN.01 (28-Oct-2019)

Amendment rationale

As of the release of this amendment, no subjects have been screened nor have received study treatment in China.

Due to regulatory restrictions on biological sample collection and testing in China, this local amendment is needed for China only, to specify that no exploratory assessments are to be done unless approval in China has been obtained by all relevant Chinese authorities. Throughout the amendment, it is stated which exploratory assessments are to be done after approval by the relevant authorities, and which are not to be done at all.

Changes to the protocol

- Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underline for insertions.
- Protocol Summary has been revised to clarify that for patients enrolled in China, the following exploratory assessments are not to be done unless approval has been obtained by all relevant Chinese authorities:

- Serum cytokine analysis
- B-cell and T cell levels
- Tisagenlecleucel cellular kinetics by flow cytometry (Blood)

For patients enrolled in China, the following exploratory assessments are not to be done at all:

- Immunophenotyping
- Exploratory analysis on tumor biopsy
- Table 2-1: clarification language has been added to refer to Sections 8.5.2 and 8.5.3 for specifics on exploratory assessments.
- Table 8-1, Table 8-2, Table 8-3, and Table 8-4 have been revised to clarify that for patients enrolled in China, the following samples are not to be collected unless approval has been obtained by all relevant Chinese authorities:

- Cytokines (serum)
- CRS assessments in peripheral blood (serum cytokines, inflammatory markers, tisagenlecleucel cellular kinetics)
- Tisagenlecleucel, cytokines, inflammatory markers and IL6R assessments in PB in patients treated with tocilizumab
- Tisagenlecleucel cellular kinetics by flow cytometry (Peripheral Blood)
- Peripheral blood (B and T cell levels)

For patients enrolled in China the following samples will not be collected:

- Immunophenotyping, Ig deep sequencing, gene expression-Peripheral Blood, and ctDNA plasma for MRD and tumor clonal analysis by Ig deep sequencing

- Tisagenlecleucel cell product sample for correlative studies
- For patients enrolled in China, tumor biopsy will not be submitted centrally for exploratory assessments; however a tumor biopsy must be done for eligibility and screening purposes with local pathology assessment.
- Table 8-5 has been updated to clarify that for patients enrolled in China: Tumor biopsy must be done for eligibility and screening purposes with local pathology assessment; however the biopsies will not be submitted centrally.
 - Table 8-8 has been updated to clarify which assessments will not be done in China.
 - Section 8.5.2 has been updated to clarify that for patients enrolled in China, flow cytometry measurements of cellular kinetics are considered an exploratory endpoint for this study. This assessment is only to be done if approval has been obtained by all relevant Chinese authorities.
 - Table 8-13 has been updated to clarify that for patients enrolled in China, flow cytometry samples are only to be collected if approval is obtained by all relevant Chinese authorities.
 - Section 8.5.3 has been updated to clarify that for patients enrolled in China, samples for B cell levels, T cell levels and serum cytokine analysis should be collected, only if approved by all relevant Chinese authorities. Samples for central tumor biopsy analysis and peripheral blood immunophenotyping, gene expression profiling, and ctDNA plasma for MRD and tumor clonal analysis by Ig deep sequencing are not to be collected in patients enrolled in China.
 - Table 8-19 and Table 8-20 have been updated to clarify that for patients enrolled in China, this sample should be collected only if approval has been obtained by all relevant Chinese authorities.
 - Table 8-21 and Table 8-22 have been updated to clarify that for patients enrolled in China, this sample will not be collected.
 - Section 10.2.6 has been updated to clarify which samples are to be collected and which ones are not to be collected unless approval has been obtained by all relevant Chinese authorities.

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

Amendment 1 (22-Feb-2019)

Amendment rationale

At the time of this amendment, no sites have yet been activated for the study.

The amendment was initiated in order to address feedback from multiple health authorities. There were several key updates that were required which could affect the conduct and management of the study:

- Modification of the cytokine release syndrome (CRS) recommendations to the most up-to-date approach on management of CRS and inclusion of neurotoxicity grading as per the America Society for Blood and Marrow Transplantation (ASBMT) consensus guidelines (Lee et al 2018)
- Introduction of a new stratification factor of region to account for variety of implementation of standard of care treatment strategy across regions
- Clarification of the crossover timelines following hematopoietic stem cell transplant (HSCT)
- Modification of serious adverse event (SAE) reporting requirement as per health authority commitment to require reporting of:
 - Progression of malignancy with fatal outcome as an SAE within 24 hours of awareness, if the following criteria are met:
 - Death within 30 days after tisagenlecleucel infusion, irrespective of causality to tisagenlecleucel
 - Death beyond 30 days after tisagenlecleucel infusion, if there is a least a possible causality to tisagenlecleucel
- Several changes to the lab collection schedule to reduce the burden of cellular kinetic/biomarker collections, and to ensure adequate safety assessments during bridging chemotherapy
- Clarifying language on the implementation of standard of care (SOC) therapy to reduce heterogeneity of arm B treatment across the study
- The week 6 timepoint was changed to PET-CT and the window was widened to ± 2 weeks and language was added to ensure that this evaluation occurs after bridging chemotherapy and prior to tisagenlecleucel infusion

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underline for insertions. Significant changes are listed below:

- Section 1.1.2 was added to describe historical experience with viral gene therapies
- Section 1.1.3 was updated with recent data on clinical experience, with new Section 1.1.3.3 on Clinical efficacy and 1.1.3.4 on Clinical safety
 - Table 2-1 was updated to:



- Clarify for all objectives whether the objective refers to Arm A and crossover, or all arms
- Combine both objectives related to immunogenicity in Arm A to one objective
- Clarify that the flow cytometry endpoint will consist only of summary of concentrations by timepoints
- Remove the exploratory objective of characterization of immunogenicity for Arm B
- Remove exploratory objective related to rituximab PK
- Clarify that exploratory objectives referring to “PFS” should refer to “EFS” since this is the primary endpoint of the study
- Section 3 was updated to:
 - Clarify that patients with historical leukapheresis product do not need to undergo a new leukapheresis collection.
 - Add a stratification factor of Region (North America vs. Rest of World)
 - Clarify that every effort should be made to bring patients in a PR to transplant
 - Clarify language that ibrutinib and lenalidomide are only to be used in patients who are no longer eligible for HSCT
 - Clarify the allowable window of response assessments to be brought in line with the Visit Evaluation Schedules. The week 6 timepoint window was also widened to ± 2 weeks to ensure that this evaluation occurs after bridging chemotherapy and prior to tisagenlecleucel infusion
- Figure 3-1 was updated to clarify the different options available after week 6 and to update week 6 to PET-CT
- Section 4.1 added a limit of 365 days after transplant was added for eligibility for crossover
- Section 4.1 removed language related to CTL019 toxicity since it is not relevant to this section
- Rationale for Lymphodepletion was moved from section 4.4 to 4.1.1
- Section 4.2 clarified that chemotherapy regimens are not recommendations, but rather these are the only allowable treatments per protocol
- Section 4.3 added Language was updated as in Section 3 to clarify that ibrutinib and lenalidomide are only to be used if the patient is no longer eligible for HSCT
- Section 4.5 was updated with language regarding contraception requirements
- Section 4.5.1.1 updated Cytokine Release Syndrome language including a definition of the date of resolution of CRS. A description of grading of CRS was inserted to a new table 4-2 (grading was previously discussed in Table 6-2).
- Section 4.5.1.2 was updated to introduce the immune effector cell-associated neurotoxicity syndrome (ICANS) grading system, including the immune effector cell-associated encephalopathy ICE score ,
- Sections 4.5.1.5, 4.5.1.5.1, 4.5.1.6, 4.5.1.7, 4.5.1.8, 4.5.2.1, 4.5.2.2, 4.5.2.3, 4.5.2.4, and 4.5.2.5 were updated with new program-standard risk language. The sections previously

labeled 4.6.1.7.1 (progressive multifocal leukoencephalopathy (PML)), 4.6.2.6 (New incidence or exacerbation of an existing neurological event), and 4.6.2.7 (graft versus host disease (GVHD)) were removed.

- Section 4.5.3.1 was updated with language on pregnancy and to allow for unscheduled quantitative polymerase chain reaction (qPCR) collections in long term additional follow-up to monitor for contraception requirements
- Section 4.5.3.2 was updated to clarify the management of SOC risks
- Section 5.1 Inclusion criteria was updated
 - Inclusion Criteria #3 was updated to clarify that in some cases a biopsy after relapse/progression is not mandatory
 - Inclusion Criteria #5 was updated to state that intention to transplant and type of high dose chemotherapy (HDCT) regimen is documented in interactive response technology (IRT) only, not in the electronic case report form (eCRF)
 - Inclusion Criteria #8 was updated with slightly different bilirubin and oxygen saturation requirements
- Section 5.2 Exclusion criteria was updated:
 - Exclusion Criteria #4 was updated to specify CNS involvement by disease under study
 - Exclusion Criteria #7 was updated to clarify as per Section 16.1 that patients with prior hepatitis B and C are allowed on study
 - Exclusion Criteria #8 was updated to remove reference to repeat testing, as this is included on the pre-infusion checklist
 - Exclusion Criteria #9 was updated with more clear language on infections
 - Exclusion Criteria #10 was updated to allow any patient with left ventricular ejection fraction (LVEF) $\geq 45\%$ at screening to be eligible for the study, regardless of testing within the past 6 months
 - Exclusion Criteria #11 was updated to clarify which prior malignancies are allowed
 - Exclusion Criteria #12 was updated to clarify that hypersensitivity to any drug product advised by the protocol is an exclusion
 - Exclusion Criteria #13 was updated to add cerebrovascular disorders
 - Exclusion Criteria #14 was changed to require a serum test, and removed reference to testing before study treatment, since this would not occur at the time of eligibility assessment
 - Exclusion Criteria #15 and #16 were updated to clarify the duration of contraception requirement for both arms
 - Exclusion Criteria #17 related to additional parallel investigational drug or device studies was removed, since this is already covered by Exclusion #6
 - Exclusion Criteria #17 (new) was added to clarify that patients who have a contraindication to study procedures should not be enrolled
- Section 6.1.1 was updated to:

- Statement was added that immunochemotherapy should start within 7 days of randomization
- State that change in therapy is required if the response does not allow the patient to proceed to transplant
- Clarify that patients should be given every possible chance to proceed to transplant
- Clarify that ibrutinib and lenalidomide are only to be used if the patient is no longer eligible for transplant
- Clarify that transplant may occur after only 3 cycles of immunochemotherapy at investigator discretion
- Add that HSCT date is recorded in IRT
- Section 6.1.2 Pre-infusion evaluation checklist:
 - Check #4
 - Language regarding repeat of viral serology testing was moved from Section 8.1, since this language refers to a check done prior to infusion
 - Added additional check for clinically significant active infection
 - Check #6 and Check #9 were added
 - Check #7 was updated with the correct section referenced
 - Check #8 was updated to clarify that any northern hemisphere country should follow October through May for influenza testing
- Section 6.1.3 was updated to allow for infection prophylaxis as per standard guidelines and the number of doses of tocilizumab that must be available after dosing was clarified
- Section 6.1.4.2 specifies that tisagenlecleucel availability should be confirmed prior to starting lymphodepleting chemotherapy, and the timing of the lymphodepleting visit in patients not receiving lymphodepleting chemotherapy was updated
- Section 6.1.5 was updated to:
 - Clarify that the tisagenlecleucel dosing is based on the viable cell count
 - Clarify that ibrutinib and lenalidomide are only to be used if the patient is no longer eligible for transplant
- Section 6.1.7 was updated to:
 - Clarify that bridging chemotherapy is part of the treatment strategy in Arm A
 - Clarify that the approved label, required country, and institution guidelines should be followed for bridging chemotherapy
 - Clarify that modifications to drug combinations of the pre-defined regimens should be approved by the Novartis global medical representative
- Section 6.2.1 was updated to refer to modified reporting criteria during certain trial periods
- Section 6.2.2 was updated to:
 - Change recommendation from referring to central nervous system (CNS) therapy to CNS prophylaxis
 - Update the recommendations for live vaccines

- Update the recommendations for myeloid growth factors
- Section 6.3.2 was updated to reflect the new stratification factor
- Section 6.5 was updated to clarify that modifications to drug combinations of the pre-defined regimens should be approved by the Novartis global medical representative
- Section 6.6.1.2 was updated to clarify that this section also applies to optional bridging immunochemotherapy and lymphodepleting chemotherapy
- Section 6.6.2.1 was updated to clarify that the availability of 4 doses of tocilizumab are required on site for each patient
- Table 6-2 was updated to separate the grading of CRS from the management (grading was moved to Table 4-2). Management recommendations were also updated
- Section 6.6.2.2 was updated to ensure ICANS grade and ICE score is used to monitor for neurotoxicity
- Section 6.6.2.4 was significantly shortened
- Section 6.6.2.5 was updated to clarify time restrictions when live virus vaccinations can be given
- Section 6.6.2.8, 6.6.2.9 and 6.6.2.10 were updated with most relevant management strategy
- Section 6.6.2.11 (GVHD) was deleted
- Section 6.6.3 was added (but described as not applicable)
- Section 6.7.1.2 was added to replace part of section 6.7.1.1 with the standard process for disposal of tisagenlecleucel.
- Section 6.7.1.3 was added to clarify handling of standard of care therapy
- Section 8 was updated to:
 - to allow the possibility of additional monitoring assessment in accordance to local practice
 - to clarify the meaning of the (*) within the VES tables
- Table 8-1 was updated to:
 - State that spirometry results are captured in the source only, not in the eCRF
 - Clarify the multiple gated acquisition (MUGA) scan is an acceptable alternative to ECHO
 - Clarify that either computed tomography (CT)/magnetic resonance imaging (MRI) of brain or lumbar puncture can be used to confirm absence of CNS disease
 - Clarify that fertility assessment is only done at screening
 - Clarify that serum pregnancy test should be done prior to leukapheresis and is source documented only
 - Remove flow cytometry for cellular kinetics assessment
 - Remove Bone marrow collections for cellular kinetics from the randomization visit
 - Immunophenotyping analyses were condensed into one row, taking from flow cytometry before leukapheresis and leukapheresis for correlative studies

- Add peripheral blood cell levels assessment at screening, since this assessment is needed for Inclusion Criteria #8c
- Table 8-2 was updated to:
 - Allow for multiple cycles of bridging chemotherapy with visits tied to cycles
 - Change the week 6 visit to PET-CT and move the Week 6 visit prior to lymphodepleting chemotherapy and after bridging chemotherapy, and widen the window to ± 2 weeks. Footnote 2 was added to specify the timing of this scan as pre-infusion.
 - Update of visit names so that they are based on the actual date of infusion rather than an assumed Day 28 infusion
 - Add requirements to repeat physical examination, ECOG, vital signs, central hematology, and central chemistry on Day 1 and 15 of each cycle of bridging chemotherapy and coagulation, pregnancy testing and weight on Day 1 of every cycle only. Urine dipstick is done on Day 1 of the first cycle only Footnote 1 was also added to clarify
 - Clarify that physical examination, performance status, and vital signs should be done at the lymphodepleting visit
 - Electrocardiogram (ECG) requirement was updated to only be on the day of infusion and otherwise as clinically indicated
 - Add ECHO/MRA/MUGA as clinically indicated
 - Add the ICANS grading and ICE score to assess neurotoxicity as per ASBMT consensus grading
 - Change the week 6 scan from CT to PET-CT
 - Clarify that CT scan is required at M6 only if PET-CT is not available
 - Clarify that either CT/MRI of brain or lumbar puncture are as clinically indicated
 - Changed cardiac enzyme testing to only as clinically indicated
 - Require serum pregnancy testing during bridging chemotherapy. Duration of testing was updated to specify monthly testing for as long as contraception is required
 - Remove rituximab PK collections
 - Clarify humoral versus cellular immunogenicity and specify that these collections are only until M12 in long term additional follow-up
 - Clarify the location of additional tables on CRS and tocilizumab-related collections
 - Remove the lymphodepleting chemotherapy and 10 minutes post-dose collection for tisagenlecleucel cellular kinetics by qPCR
 - Significantly reduce the frequency of tisagenlecleucel cellular kinetics by flow cytometry collections
 - Remove tisagenlecleucel cellular kinetics in bone marrow by flow cytometry, and reduce frequency of qPCR collections
 - Add cerebral spinal fluid (CSF) collections for tisagenlecleucel for cellular kinetics by qPCR as clinically indicated (this was already described in Section 8.5.2)
 - Remove lab collections from survival follow-up visit

- Remove ePRO from the week 8 (Infusion + 28d) visit
- Add a footnote to explain the meaning of * as being related to the day of tisagenlecleucel infusion, in addition to footnotes on repeating of bridging chemotherapy cycles and the week 6 scan
- Table 8-3 was updated to:
 - Allow for multiple cycles of SOC chemotherapy. Safety visits will be tied to the cycles of chemotherapy rather than to randomization.
 - Add visits related to HSCT with safety assessments, including conditioning, HSCT day, and HSCT +7, 14, 21, and 28 days
 - Widen the window for the week 6 visit to ± 2 weeks and change from CT to PET-CT
 - Add section headers to describe the types of assessments listed below each section
 - Add requirements to repeat physical examination, ECOG, vital signs, central hematology, and central chemistry on Day 1 of each cycle of bridging chemotherapy and coagulation, pregnancy testing and weight on Day 15 of every cycle. Footnote 1 was also added to clarify
 - Add M18 performance status assessment
 - Change requirement of ECG, cardiac enzymes, and ECHO/MRA/MUGA to as clinically indicated, and then repeated at crossover
 - Clarify that CT scan is required at M9 and M12, and only at M6 if PET-CT is not available
 - Clarify that either CT/MRI of brain or lumbar puncture are as clinically indicated
 - Update pregnancy testing during chemotherapy treatment to be with serum testing
 - Specify the duration of pregnancy testing to be monthly throughout the study until the end of contraception requirements per local label
 - Add viral serology testing at the crossover visit
 - Add peripheral blood B cell levels to the table (to align with the collections as described in Sections 8.5.2.1 and Section 8.5.3)
 - ePRO was removed from the Week 8 visit, as the Week 8 visit no longer exists
 - Footnote was added to clarify repeating of immunochemotherapy cycles
- Table 8-4 was updated to:
 - Allow for multiple cycles of bridging chemotherapy with visits tied to cycles
 - Change the week 6 visit to PET-CT and move the Week 6 visit prior to lymphodepleting chemotherapy and after bridging chemotherapy, and widen the window to ± 2 weeks. Footnote 2 was added to specify the timing of this scan, which may be prior to tisagenlecleucel infusion or after depending on the availability of product.
 - Update of visit names so that they are tied to the date of infusion rather than an assumed Day 28 infusion
 - Add requirements to repeat physical examination, ECOG, vital signs, central hematology, and central chemistry on Day 1 of each cycle of bridging chemotherapy

- and coagulation, pregnancy testing and weight on Day 15 of every cycle. Footnote 1 was also added to clarify
- Clarify that physical examination, performance status, and vital signs should be done at the lymphodepleting visit
 - Update ECG requirement to be only on the day of infusion and as clinically indicated
 - Add ECHO/MRA/MUGA as clinically indicated
 - Add the ICANS grading and ICE score to assess neurotoxicity as per ASBMT consensus grading
 - Changed cardiac enzyme testing to only as clinically indicated
 - Duration of pregnancy testing was updated to specify monthly testing for as long as contraception is required
 - Remove Rituximab PK collections\
 - Clarify humoral versus cellular immunogenicity and specify that these collections are only until M12 in long term additional follow-up
 - Significantly reduce the frequency of flow cytometry for cellular kinetics collections
 - Remove lab collections from the survival follow-up visits
 - Remove tisagenlecleucel cellular kinetics in bone marrow by flow cytometry, and reduce frequency of qPCR collections
 - Add CSF collections for tisagenlecleucel for cellular kinetics by qPCR as clinically indicated (to align with the collections as described in Section 8.5.2)
 - Add serum cytokine collections, CRS assessments, and collections for patients treated with tocilizumab (this was already described in Section 8.5.2.1 and 8.5.3)
 - Remove ePRO from the week 8 (Infusion + 28d) visit and from Day 1
 - Add a footnote to explain the meaning of * as being related to the day of tisagenlecleucel infusion, in addition to footnotes on repeating of bridging chemotherapy cycles and the week 6 scan
 - Section 8.1 was updated to:
 - Remove language on repeat viral serology testing before infusion, as it was added to section 6.1.2
 - Clarified that serum pregnancy testing is required prior to leukapheresis
 - Align pre-leukapheresis lab values with Inclusion Criteria #8
 - Clarify that only patients who are having manufacture of tisagenlecleucel will send the leukapheresis material to the manufacturing facility
 - Section 8.1.1 was updated to clarify the timing of information on leukapheresis being sent to the manufacturing facility, to clarify that the assessment of eligibility is by investigator judgement, and to add language on the new stratification factor
 - Section 8.3 was updated to:
 - Clarify that all randomized patients (even those that don't receive study treatment) should have efficacy assessments, and that all patients should have an efficacy assessment prior to starting new anticancer therapy

- Added language on patients who have stable disease (SD)/progressive disease (PD) at the Week 12 visit, while they are still waiting for tisagenlecleucel infusion
- Clarified allowable methods of CNS disease assessment
- Change the Week 6 scan from CT to PET/CT
- Clarify the timing of the Week 6 assessment in Arm A, Arm B, and crossover patients
- Clarify which scan should be treated as the baseline for patients that crossover to arm A
- Clarify in table 8-5 that there is only one tumor biopsy required at screening, and that week 6 is PET-CT
- Update table 8-5 to include the option of brain CT/MRI or lumbar puncture mandated at baseline
- Section 8.3.3 was updated to:
 - Simplify language regarding the need for expedited review
 - Update the window of week 6 to +/- 2 weeks
 - Add a limit of 365 days after transplant was added for eligibility for crossover
 - Clarify what should occur after an investigator submits a scan for SD/PD confirmation, based on the blinded independent review committee (BIRC) response
- Table 8-8 was split into Table 8-8 and Table 8-9 which specifies which assessments are done locally and which are central
- Section 8.4.2.2 was updated to change the timing of cardiac enzyme collection
- Section 8.4.3 was updated to simplify language on pregnancy
- Section 8.5.2 was updated to:
 - Remove Rituximab PK
 - Clarify that qPCR will be the main endpoint for cellular kinetics, with only summary data for flow cytometry
 - Clarify that patients who crossover will also be assessed for cellular kinetics
- Table 8-11 was updated to remove Rituximab PK
- Table 8-12 was updated with new visit naming as per VES, and with new scheduled timepoint relative to infusion, and lymphodepleting and 10 minutes post-dose collection was removed. A footnote was also added to clarify the collection of qPCR samples for monitoring of contraception requirements.
- Table 8-13 was updated to significantly reduce the frequency of flow cytometry collections and with new visit naming as per VES, and new scheduled timepoint relative to infusion
- Table 8-14 was updated to reduce the frequency of collection, and update new scheduled timepoint relative to infusion for qPCR bone marrow collections
- The table on bone marrow flow cytometry for cellular kinetics was removed
- Table 8-15 was updated to reduce the frequency of collection

- Table 8-16 was updated with new visit naming as per VES, and with new scheduled timepoint relative to infusion and clarified to refer to humoral testing. Sample numbers for long term additional follow-up were clarified in a footnote
- Table 8-17 was updated with new visit naming as per VES, and with new scheduled timepoint relative to infusion and clarified to refer to cellular testing. Sample numbers for long term additional follow-up were clarified in a footnote.
- The table on Rituximab PK was removed
- Section 8.5.3 was updated to clarify the requirements for tumor biopsy
- Table 8-19 was updated with new visit naming as per VES
- Table 8-20 was updated to clarify the timing of B cell level collection and update visit naming as per VES
- Table 8-21 was updated with new visit naming as per VES
- Table 8-22 was updated with new visit naming as per VES and clarified that chimeric antigen receptor (CAR) expression is also measured on the tumor biopsy if available. It was also clarified that the timepoint just after infusion is optional
- Section 9.1.5 updated language on early study termination
- Section 10.1.1 removed language on reporting of disease progression as an SAE, and updated language on changes to study treatment . The language on when standard versus modified reporting of adverse events (AEs) would be required as per study period was also clarified and condensed. A new statement was added to allow for collection of key components of CRS events to allow for grading in alternative grading scales
- Section 10.1.2 was updated with new language on reporting of disease progression as an SAE
- Section 10.1.4 was also added to allow for SAE reporting as per health authority request
- Section 10.1.5 was updated with pregnancy reporting requirements
- Section 10.2.3 was updated to clarify that the DMC will not assess efficacy
- Section 12.1 was updated to align with the CTL019 Project statistical analysis plan (SAP). A new “infused set” was defined, and the safety set was clarified. The anti-cytokine PK set was removed, since this assessment is not done in this study
- Section 12.4.1 was updated to allow for a definition of the week 12 assessment window to be included in the SAP rather than the protocol
- Section 12.4.2 was updated with clarifying language on the hypothesis and stratification
- Section 12.4.3 was updated to remove missing tumor assessment as a censoring reason, and the definition of new anticancer therapy was clarified to also include any anti-neoplastic therapy given after HSCT
- Section 12.4.4 was updated to clarify the log-rank tests to be used, to add a sensitivity analysis counting missing assessment as a censoring reason, and to add all stratification factors as subgroup analyses as well. In addition, a sensitivity analysis for event free survival(EFS) per BIRC irrespective of new anti-cancer therapy for lymphoma was added
- Section 12.5 was updated with the new stratification factor, define the maximum time for crossover, and to further explain potential methods for overall survival (OS) sensitivity

analysis. A further sensitivity analysis for overall response rate (ORR) was added using evidence of disease at the Week 6 assessment.

- Section 12.5.2 was updated to align with the project level CTL019 SAP with clarification of safety time periods and analysis. A sensitivity analysis was also added for grading of CRS and neurotoxicity on alternative grading scales (e.g. ASBMT)
- Section 12 removed all reference to rituximab PK and tocilizumab PK
- Section 15 references were added/remove as appropriate
- Section 16.1 was updated with new eligibility algorithms for hepatitis B and C.
- Section 16.3 was updated with new modified reporting requirements, and also clarified that standard reporting resumes again for patients that crossover to arm A

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.



Protocol summary

Protocol number	CCTL019H2301
Full Title	Tisagenlecleucel versus standard of care in adult patients with relapsed or refractory aggressive B-cell non-Hodgkin lymphoma: A randomized, open label, phase III trial (BELINDA)
Brief title	Tisagenlecleucel in adult patients with aggressive B-cell non-Hodgkin lymphoma
Sponsor and Clinical Phase	Novartis - Phase III
Investigation type	Biological
Study type	Interventional
Purpose and rationale	<p>Current front-line therapies for diffuse large B-cell lymphoma (DLBCL) and other aggressive B-cell non-Hodgkin lymphoma (NHL) (e.g. Follicular lymphoma grade 3B (FL3B), primary mediastinal large B cell lymphoma (PMBCL), T cell rich/histiocyte rich large B cell lymphoma, DLBCL associated with chronic inflammation, intravascular large B-cell lymphoma, anaplastic lymphoma kinase positive (ALK+) large B-cell lymphoma) consist of combination chemotherapies with CD20-targeted immunotherapies. While over 50% of patients reach long-lasting complete response (CR) with initial therapy, approximately one-third of patients are refractory (i.e. do not achieve a response) to therapy or will relapse or progress after initial response. These patients have poor prognosis, especially if they are refractory or have an early relapse (i.e., within 12 months of last therapy) even if the patient receives high dose chemotherapy and autologous hematopoietic stem cell transplant (HSCT). Novel therapies for relapsed/refractory (r/r) DLBCL and other aggressive B-cell lymphomas are highly needed.</p> <p>The B-cell marker CD19 has emerged as a target for B-cell lymphoma treatment in the past years. It is widely expressed on normal and malignant B-cells throughout B-cell maturation but not on pluripotent stem cells or non-B-cell tissues. The vast majority of DLBCL expresses CD19 (Kimura et al 2007). Targeting CD19 by chimeric antigen receptor (CAR) T cell therapy has been shown to be effective at eradicating malignant cells from very advanced B-cell malignancies and to have the potential to induce durable complete responses in patients lacking effective treatment options. Data from patients with B-cell Acute Lymphoblastic Leukemia (ALL), Chronic Lymphocytic Leukemia (CLL), and other CD19 expressing B cell lymphomas show that tisagenlecleucel therapy has potent anti-tumor activity.</p> <p>This phase III study will compare the efficacy and safety of tisagenlecleucel treatment strategy against the current SOC (standard second line salvage chemotherapy including autologous HSCT in suitable patients), in poor prognosis patients with aggressive B-cell NHL after failure of frontline rituximab- and anthracycline-based therapy.</p> <p>The two treatment strategies being compared are</p> <ul style="list-style-type: none">• Tisagenlecleucel after optional bridging chemotherapy and lymphodepleting (LD) chemotherapy• Standard of care chemotherapy followed by autologous HSCT
Primary Objective	The primary objective of this study is to compare tisagenlecleucel treatment strategy to SOC treatment strategy with respect to delaying the composite event of disease progression(PD)/stable disease (SD) at or after the Week 12 assessment; or death at any time, i.e. event free survival (EFS) as assessed by a blinded independent review committee (BIRC).

<p>Secondary Objectives</p>	<ul style="list-style-type: none"> • To compare tisagenlecleucel treatment strategy to SOC treatment strategy with respect to EFS by local investigator. • To compare tisagenlecleucel treatment strategy to SOC treatment strategy with respect to overall survival (OS). • To compare tisagenlecleucel treatment strategy to SOC treatment strategy with respect to overall response rate (ORR) and duration of response (DOR) by BIRC and local investigator. • To compare tisagenlecleucel treatment strategy and SOC treatment strategy with respect to time to response (TTR). • To evaluate safety and tolerability of tisagenlecleucel treatment strategy versus SOC treatment strategy. • To compare patient reported outcomes (PROs) of health-related quality of life (HRQoL) in both treatment arms. • Evaluate efficacy and safety of both treatment arms in histological subgroups (e.g DLBCL, not otherwise specified (NOS), FL3B, other) and molecular subgroups (e.g. germinal center B-cell (GCB), activated B-cell (ABC), other) • To assess the patients treated with tisagenlecleucel (in Arm A or after crossover) treatment strategy with respect to the following objectives: <ul style="list-style-type: none"> • Characterize the in vivo cellular kinetics of tisagenlecleucel transduced cells into target tissues (blood, bone marrow, cerebral spinal fluid (CSF) and other tissues if available), as measured by quantitative polymerase chain reaction (qPCR) summarized by clinical response in patients receiving tisagenlecleucel therapy in arm A or after crossover. To characterize the incidence and prevalence of tisagenlecleucel immunogenicity (humoral and cellular) and impact on cellular kinetics, efficacy, and safety in patients receiving tisagenlecleucel therapy in arm A or after crossover • Assess presence of replication competent lentivirus (RCL) in patients receiving tisagenlecleucel in Arm A or after crossover.
<p>Study design</p>	<p>This is a randomized, open label, multicenter phase III trial comparing the efficacy, safety, and tolerability of tisagenlecleucel to SOC in adult patients with aggressive B-cell NHL after failure of rituximab and anthracycline containing first line immunochemotherapy. Failure of frontline therapy is defined as refractoriness (lack of complete response or progression during therapy) or relapse/progression within 365 days of last dose of first line therapy (in patients who achieved CR on first line therapy).</p> <p>The randomized China extension cohort will continue recruitment separately from the global study main cohort if the number of participants from China mainland in the global study main cohort is not sufficient to support registration in China. The additional cohort will allow recruitment to continue in China mainland until 36 participants have been randomized in order to support registration in China.</p> <p>Screened patients may undergo non-mobilized leukapheresis for autologous T cell collection soon after obtaining informed consent (unless historical product is to be used). During the screening period, no lymphoma-specific therapy is allowed prior to randomization. During randomization, patients will be stratified by:</p> <ol style="list-style-type: none"> (a) Remission duration - refractory to front line therapy or relapsed < 6 months from last dose of first line immunochemotherapy v. relapsed 6 - 12 months) (b) International prognostic index (IPI) score (< 2 versus ≥ 2) based on central labs and as per treating physician's assessment at study entry, The International Non-Hodgkin's Lymphoma Prognostic Factors Project (1993); Moskowitz (1999). (c) Region (North America vs Rest of World) <p>Eligible patients will be randomized into:</p> <p>Arm A: (tisagenlecleucel treatment strategy): Patients will receive lymphodepletion chemotherapy followed by infusion of tisagenlecleucel. Use</p>

	<p>of platinum-based bridging chemotherapy prior to lymphodepletion therapy is allowed.</p> <p>Arm B: (standard of care treatment strategy): Patients will receive platinum-based immunochemotherapy, followed in responding patients by HDCT and autologous HSCT.</p> <p>Tumor and response assessments will be performed during the screening period (baseline within 2 weeks of randomization), 6 weeks after randomization (\pm 2 weeks), 12 weeks after randomization (\pm 1 week), 6 months after randomization (\pm 2 weeks), every 3 months thereafter (\pm 2 weeks) for the first year, every 6 months (\pm 2 weeks) for the second year, and annually thereafter (\pm 2 weeks) up to 5 years after randomization.</p> <p>Crossover from arm B to arm A is allowed after confirmed SD/PD by BIRC at any time at or after the Week 12 assessment up until 1 year after autologous HSCT.</p>
Population	<p>The global study main cohort will randomize approximately 318 patients age 18 or greater. The study has the option to extend recruitment beyond 318 patients in order to randomize at least 36 participants from China mainland to support registration in China.</p>
Key Inclusion criteria	<ol style="list-style-type: none"> 1. Histologically confirmed (by local histopathological assessment), aggressive B-cell NHL at relapse/progression or PR after front line therapy. For patients with relapse/progression if biopsy after relapse/progression is not available or it is not clinically feasible to obtain a new biopsy, an archival tumor biopsy from the initial diagnosis may be submitted. For patients in PR after at least 6 cycles of first line treatment, a new biopsy must be submitted. Aggressive B-cell NHL is heretofore defined by the following list of subtypes (Swerdlow et al 2016): <ul style="list-style-type: none"> • DLBCL, NOS, • FL grade 3B, • Primary mediastinal large B cell lymphoma (PMBCL), • T cell rich/histiocyte rich large B cell lymphoma (T/HRBCL), • DLBCL associated with chronic inflammation, • Intravascular large B-cell lymphoma, • ALK+ large B-cell lymphoma, • B-cell lymphoma, unclassifiable, (with features intermediate between DLBCL and classical Hodgkin Lymphoma (HL)), • High grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements, • High-grade B-cell lymphoma, NOS • HHV8+ DLBCL, NOS • DLBCL transforming from follicular lymphoma • DLBCL transforming from marginal zone lymphoma • DLBCL, leg type 2. Relapse or progression within 365 days from last dose of anti-CD20 antibody and anthracycline containing first line immunochemotherapy or refractory (have not achieved a CR). 3. Patient is considered eligible for autologous HSCT as per local investigator assessment. Note: Intention to transplant and type of high dose chemotherapy (HDCT) regimen will be documented in the Interactive Response Technology (IRT) system. 4. Disease that is both active on PET scan (defined as Deauville score of 4 or 5) and measurable on CT scan defined as: <ol style="list-style-type: none"> a. Nodal lesions >15 mm in the long axis, regardless of the length of the short axis, and/or b. Extranodal lesions (outside lymph node or nodal mass, but including liver and spleen) >10 mm in long AND short axis 5. Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1

	<p>6. Adequate organ function:</p> <p>Renal function defined as:</p> <ul style="list-style-type: none"> a. Serum creatinine of $\leq 1.5 \times$ upper limit of normal (ULN), OR estimated glomerular filtration rate (eGFR) ≥ 60 mL/min/1.73 m² <p>Hepatic function defined as:</p> <ul style="list-style-type: none"> b. Alanine Transaminase (ALT) and Aspartate Transaminase (AST) $\leq 5 \times$ ULN c. Total Bilirubin $\leq 1.5 \times$ ULN with the exception of patients with Gilbert syndrome who may be included if their total bilirubin is $\leq 3.0 \times$ ULN and direct bilirubin $\leq 1.5 \times$ ULN <p>Hematologic Function (regardless of transfusions) defined as:</p> <ul style="list-style-type: none"> d. Absolute neutrophil count (ANC) $> 1000/\text{mm}^3$ e. Platelets $\geq 50,000/\text{mm}^3$ f. Hemoglobin > 8.0 g/dl <p>Only for patients with non-historical apheresis:</p> <ul style="list-style-type: none"> g. Absolute lymphocyte count (ALC) $> 300/\text{mm}^3$ or h. Absolute number of CD3+ T cells $> 150/\text{mm}^3$ <p>Adequate pulmonary function defined as:</p> <ul style="list-style-type: none"> i. No or mild dyspnea (\leq Grade 1) j. Oxygen saturation measured by pulse oximetry $> 90\%$ on room air k. Forced expiratory volume in 1 s (FEV1) $\geq 50\%$ or carbon monoxide diffusion test (DLCO) $\geq 50\%$ of predicted level <p>7. Must have a leukapheresis material of non-mobilized cells available for manufacturing. Note: Please refer to Section 6.2.2, Section 8.1 (Leukapheresis) for prohibited concomitant medications and washout times to ensure adequate collection as well as the [Investigational Leukapheresis, Cryopreservation and Scheduling Manual] for specific collection procedures.</p>
Key Exclusion criteria	<ul style="list-style-type: none"> 1. Prior treatment with anti-CD19 therapy, adoptive T cell therapy, or any prior gene therapy product 2. Treatment with any systemic lymphoma-directed second line anticancer therapy prior to randomization. Only steroids and local irradiation are permitted for disease control. 3. Patients with active central nervous system (CNS) involvement by disease under study are excluded, except if the CNS involvement has been effectively treated and local treatment was > 4 weeks before randomization 4. Prior allogeneic HSCT 5. Uncontrolled acute life threatening infection 6. Any of the following cardiovascular conditions: <ul style="list-style-type: none"> a. Unstable angina, myocardial infarction, coronary artery bypass graft (CABG), or stroke within 6 months prior to screening, b. Left ventricle ejection fraction (LVEF) $< 45\%$ as determined by echocardiogram (ECHO) or magnetic resonance angiography (MRA) or multigated acquisition (MUGA) at the screening assessment. c. New York Heart Association (NYHA) functional class III or IV (Chavey et al 2001), at screening or within the past 12 months. d. Clinically significant cardiac arrhythmias (e.g., ventricular tachycardia), complete left bundle branch block, high-grade atrioventricular (AV) block (e.g., bifascicular block, Mobitz type II) and third degree AV block unless adequately controlled by pacemaker implantation. e. Resting QTcF ≥ 450 msec (male) or ≥ 460 msec (female) at screening or inability to determine the QTcF interval f. Risk factors for Torsades de Pointes (TdP), including uncorrected hypokalemia or hypomagnesemia, history of cardiac failure, or history of clinically significant/ symptomatic bradycardia, or any of the following:

	<ul style="list-style-type: none"> i. Long QT syndrome, family history of idiopathic sudden death or congenital long QT syndrome ii. Concomitant medication(s) with a “Known Risk of Torsades de Pointes” per crediblemeds.org that cannot be discontinued or replaced by safe alternative medication. <p>7. Patients with active neurological autoimmune or inflammatory disorders (e.g., Guillain-Barré Syndrome (GBS), Amyotrophic Lateral Sclerosis (ALS)) and clinically significant active cerebrovascular disorders (e.g., cerebral edema, posterior reversible encephalopathy syndrome (PRES))</p>
Study treatment	<ul style="list-style-type: none"> • Arm A: A single dose of $0.6 \text{ to } 6.0 \times 10^8$ of CAR-positive viable autologous tisagenlecleucel transduced T cells administered via i.v. infusion after optional bridging chemotherapy and LD chemotherapy • Arm B: SOC with intent to transplant (autologous HSCT) per local guidelines
Efficacy assessments	<ul style="list-style-type: none"> • Imaging (CT or MRI, PET-CT or PET), 6 weeks after randomization (± 2 weeks), 12 weeks after randomization (± 1 week), 6 months after randomization (± 2 weeks), and every 3 months thereafter (± 2 weeks) for the first year, every 6 months (± 2 weeks) for the second year, and annually thereafter (± 2 weeks) up to 5 years after randomization, • physical examination • bone marrow biopsy
Biomarker assessments	<ul style="list-style-type: none"> • Serum cytokine analysis* • B-cell and T cell levels* • Immunophenotyping** • Exploratory analysis on tumor biopsy** <p>* For patients enrolled in China: exploratory assessments are not to be done unless approval has been obtained by all relevant Chinese authorities.</p> <p>**For patients enrolled in China: these assessments will not be done.</p>
Pharmacokinetic assessments	<ul style="list-style-type: none"> • Cellular kinetics by flow cytometry (blood)* • Cellular kinetics by qPCR (blood, bone marrow, CSF if available) • Immunogenicity (blood) <p>* For patients enrolled in China: exploratory assessments are not to be done unless approval has been obtained by all relevant Chinese authorities.</p>
Key safety assessments	<p>Adverse events (AEs and laboratory abnormalities (type, frequency and severity)). All patients treated with tisagenlecleucel will be monitored for specific toxicities for up to a total of 15 years post infusion, irrespective of their response to tisagenlecleucel. All patients who receive tisagenlecleucel will be monitored in this trial for 5 years after randomization, followed by semiannual and annual safety assessments in a separate long-term follow-up protocol (CCTL019A2205B) for an additional ten years. All patients not receiving tisagenlecleucel will be followed for safety until 56 days after the last dose of study treatment. Adverse event collection will restart upon crossover for patients that crossover to arm A.</p>
Other assessments	<ul style="list-style-type: none"> • Time to definitive deterioration in 36 item short form health survey (SF-36v2), Functional Assessment of Cancer Therapy Lymphoma (FACT-Lym), and EuroQol Visual Analogue Scale (EQ-VAS)
Data analysis	<p>Approximately 318 patients and any additional China extension patients will be randomized in a 1:1 ratio to either tisagenlecleucel therapy or SOC therapy. During randomization, patients will be stratified by:</p> <ul style="list-style-type: none"> a. remission duration (refractory to front line therapy or relapsed <6 months v. relapsed at 6 -12 months inclusive) b. International prognostic index score (IPI, <2 versus ≥ 2). c. Region (North America vs. Rest of World) <p>Analysis sets:</p> <ul style="list-style-type: none"> • The Full Analysis Set (FAS) comprises all randomized patients. According to the intent to treat principle, patients will be analyzed according to the

	<p>treatment and strata they have been assigned to during the randomization procedure.</p> <ul style="list-style-type: none">• The Safety Set includes all patients to whom study treatment has been assigned by randomization. Patients will be analyzed according to randomized treatment.• The cellular kinetic analysis set consists of all patients who receive at least one dose of tisagenlecleucel and for whom at least one concentration value was available. <p>Statistical analysis: The primary endpoint is event free survival (EFS), defined as the time from the date of randomization to the date of the first documented disease progression or stable disease at or after the week 12 assessment by BIRC or death at any time. The primary efficacy objective is considered to be met if the null hypothesis, i.e. the survival functions for EFS in the two arms are identical, can be rejected based on a one-sided stratified log-rank test at 2.5% level of significance. Distribution of EFS will be estimated using the Kaplan-Meier method. The median EFS along with 95% confidence intervals (CIs) will be presented by treatment group. The Cox regression model stratified by the randomization stratification factors will be used to estimate the hazard ratio (HR) of EFS, along with the 95% confidence interval. There will be no interim analysis for EFS. The analysis for EFS will be performed when at least 200 EFS events in the FAS have been documented by the BIRC. The primary analysis of EFS for Chinese participants will be based on Chinese participants in the FAS of the global study as well as Chinese participants to whom study treatment has been assigned by randomization in the China extension cohort. The analysis will be performed after 18 EFS events have been observed in Chinese participants. The analysis will be conducted as for the global cohort, except that the log-rank test will not be performed and the region stratification factor is not applicable.</p> <p>Sample size: The 9 month EFS rate is estimated to be 22.32% in SOC arm based on the ORCHARRD study and is assumed to be 40% in tisagenlecleucel arm. Due to delayed tisagenlecleucel infusion of 6 weeks and ignoring SD/PD at week 6, we assume piecewise hazard rate in both treatment arms. The hazard ratio between two arms during the first 6 weeks is assumed to be 1 and 0.61 after 6 weeks. Given those assumptions, a total of 200 EFS events are required to have 92% power at an one-sided 2.5% level of significance to reject the null hypothesis (i.e. the survival functions for EFS in the two arms are identical), using a stratified log-rank test with equal weights.</p> <p>Considering a recruitment period of approximately 21 months using staggered enrollment rate of 2, 10, 16 patients in the first 3 months followed by 17 patients thereafter, and assuming 15% drop out rate, a total of approximately 318 patients will need to be randomized to the two treatment arms in a 1:1 ratio.</p> <p>Overall survival (OS) is a secondary endpoint and is defined as the time from date of randomization to date of death due to any cause will only be formally tested between the two treatment arms, if the primary endpoint (EFS by BIRC) is significant. A maximum of two analyses are planned for OS: i) an interim analysis at the time of the primary analysis for EFS (provided EFS is significant) and ii) a final analysis approximately 5 years after randomization of the first patient if OS is not significant at the time of the primary analysis. The median OS along and the proportion of patients alive at 6, 12 weeks, 6, 12, 18, 24, 36, 48, 60 months with 95% CIs will be presented by treatment group. OS will be compared between the two treatment groups using a log-rank test stratified by randomization stratification factors.</p> <p>Safety: The assessment of safety will be based mainly on the incidence rates of AEs, their severity and seriousness, and laboratory assessments. Other safety data (e.g., physical assessments, electrocardiograms (ECGs), vital signs) will be summarized. For all comparative safety analyses, the safety set will be used.</p> <p>Patient reported outcomes: Time to definitive deterioration for SF-36 v2 (physical and mental components), FACT-Lym (general score [G], lymphoma subscale [LymS], trial outcome index [TOI], total score [TS]), and EQ-VAS will be summarized using Kaplan-Meier methods. The estimated Kaplan-Meier plots will</p>
--	---

	<p>be provided and the unstratified log-rank test will be the primary method to compare the time to first deterioration between the two treatment groups. For SF-36 v2, a score decrease of 3 points or higher must be held to be considered "deteriorated". For FACT-Lym, a score decrease of 3 points or higher in FACT-G, 2.9 points or higher in LymS, 5.5 points or higher in TOI, and 6.5 points or higher in TS must be held to be considered "deteriorated" For EQ-VAS, a score decrease of 7 points or higher must be held to be considered "deteriorated".</p> <p>Summary statistics will be reported for each of items and scales over time by treatment arm. Repeated measures mixed-effects model will be carried to compare the two groups with respect to the change from baseline. Rates of improvement will be evaluated from baseline to each time point and will be compared between the two treatment groups using chi-square test. For the Euroqol 5 dimension (EQ-5D) health state profiles, the proportions of patients reported having "no", "slight", "moderate", "severe", or "extreme" problems at each time point will be reported.</p> <p>Cellular kinetics: Descriptive statistics will be summarized by month 3 response for all patients who receive tisagenlecleucel.</p> <p>Cellular kinetics in patients that receive tocilizumab for CRS management: For patients who received tocilizumab for cytokine release syndrome (CRS) management, the concentrations (transgene levels of tisagenlecleucel) will be summarized by time points, relative to time of tocilizumab dose. The cellular kinetic parameters will be presented with and without the use of tocilizumab.</p>
Key words	Relapsed/refractory, NHL, tisagenlecleucel, CTL019

1 Introduction

1.1 Background

1.1.1 Overview of disease pathogenesis, epidemiology and current treatment

Non-Hodgkin Lymphomas (NHL) comprise a heterogeneous group of malignancies. Estimated new cases are 72,240 and deaths are 20,140 in the United States (US) for 2017 ([Siegel et al 2017](#)). In Europe, for 2012, there were an estimated 93,500 new cases and 37,800 deaths due to NHL ([Ferlay et al 2015](#)).

The 2008 World Health Organization (WHO) classification of hematopoietic and lymphoid tumors ([Jaffe 2009](#)), updated in 2016 ([Swerdlow et al 2016](#)), represents the established guidelines for the diagnosis of malignant lymphomas. The classification is based on the recognition of distinct diseases according to a combination of morphology, immunophenotype, genetic, molecular, and clinical features. Lymphoid neoplasms are stratified according to cell lineage and derivation from precursor or mature lymphoid cells into: immature lymphoid neoplasms, mature B-cell neoplasms, T cell and natural killer (NK)-cell neoplasms, and post-transplant lymphoproliferative disorders (PTLD). Mature B-cell lymphomas are further classified into indolent lymphomas (e.g. multiple myeloma, follicular lymphoma – except for FL3B that is considered as an aggressive subtype-) and aggressive lymphomas (e.g. diffuse large B-cell lymphoma [DLBCL], Burkitt lymphoma, primary mediastinal large B cell lymphoma [PMBCL], T cell rich/histiocyte rich large B cell lymphoma [T/HCBCL], DLBCL associated with chronic inflammation, intravascular large B-cell lymphoma, ALK+ large B-cell lymphoma). DLBCL is the most frequent lymphoma subtype, representing 30-40% of all NHLs for western countries ([Chiappella et al 2016](#), [Al-Hamadani et al 2015](#)). Estimated incidence in the European Union is 3.8/100,000/year, increasing with age (reaching a maximum after 75 years) and with considerable variation across European countries ([Sant et al 2010](#), [Tilly et al 2015](#)). For the US, the incidence for the 2002-2011 period of was 6.9/100,000/year; also increasing with age (32.7/100,000/year after 65 years) ([Howlader et al 2011](#)).

The prognosis of patients with DLBCL and other B-cell aggressive lymphomas depends on individual risk factors. The International Prognostic Index (IPI) for aggressive NHL includes five risk factors independently prognostic of overall survival (OS) ([The International Non-Hodgkin's Lymphoma Prognostic Factors Project 1993](#)):

- Patient age (≤ 60 years vs. > 60 years)
- Serum lactate dehydrogenase (LDH) (normal $\leq 1 \times \text{ULN}$ vs. elevated $> 1 \times \text{ULN}$)
- ECOG performance status (0 or 1 vs. ≥ 2)
- Stage (stage I or stage II vs. stage III or stage IV)
- Extranodal site involvement (0 or 1 vs. 2–4)

Patients with ≥ 2 risk factors after age-adjustment have a poor prognosis with a 5 year OS rate of 21-46%. Age- and stage-adjusted modifications from diagnosis are used for younger patients with localized disease ([Moller et al 2003](#)). A revised IPI, the National Comprehensive Cancer Network International Prognostic Index (NCCN-IPI), has been proposed to better reflect the

individual patient's risk in the rituximab era ([Zhou et al 2014](#)). Very similar to the original IPI, five prognostic factors were identified:

- Patient age (>40 to ≤ 60 vs. >60 to ≤ 75 vs. >75 years)
- Normalized serum LDH (>1 to ≤ 3 vs. $>3 \times \text{ULN}$)
- ECOG performance status (0 or 1 vs. 2–4)
- Ann Arbor Stage (stage I or stage II vs. stage III or stage IV)
- Extranodal site involvement, that is, disease in bone marrow, CNS, liver/gastrointestinal (GI) tract, or lung (yes vs. no)

The NCCN-IPI can discriminate four prognostic groups: low (0-1), low-intermediate (2-3), high-intermediate (4-5), and high (6-8).

DLBCL is a heterogeneous disease with several molecular subtypes based on gene expression profiling (GEP) and based on biologic similarity to normal stages of B-cell development classified into: i) germinal center-B-cell-like (GCB; CD10+, or BCL6+, IRF4/MUM1-), ii) activated B-cell-like (ABC), iii) primary mediastinal large B cell lymphoma (PMBCL) and iv) type 3 (unclassifiable) DLBCL ([Swerdlow et al 2016](#), [Lenz et al 2008](#), [Alizadeh et al 2000](#)). The GCB and ABC subtypes arise from B-cells at different stages of differentiation (GCB originates from germinal center B-cells, whereas ABC arises from post-germinal-center B-cells transitioning into plasma cells) and differ in their clinical outcome. GEP is not routinely used, however, immunohistochemistry (IHC)-based algorithms predict a 5-year OS of 76% in GCB tumors compared to 34% in ABC tumors ([Hans et al 2004](#)). Indeed, inferior survival for ABC DLBCLs was also observed in patients treated with rituximab and CHOP chemotherapy ([Lenz et al 2008](#)).

Frontline treatment of patients with newly diagnosed DLBCL and other B-cell aggressive NHL is generally tailored based on age, age-adjusted IPI and feasibility of dose intensified approaches ([Tilly et al 2015](#)). The combination of rituximab (anti-CD20) with anthracycline-based chemotherapy (e.g., cyclophosphamide, doxorubicin, vincristine and prednisone [R-CHOP]) given every 21 days represents the standard frontline treatment for most patients with DLBCL. Despite most patients being cured with conventional frontline immunochemotherapy, around one-third will not respond (i.e., will not achieve a CR or PR) or will relapse or progress after treatment. More than half of all these treatment failures include non-responding and relapsing patients within a year after the standard frontline immunotherapy (early relapsed). These patients have a poor prognosis, particularly those who do not respond to second-line chemotherapy ([Sarkozy and Coiffier 2015](#), [Coiffier et al 2016](#), [Friedberg 2011](#), [Elstrom et al 2010](#)). Patients who achieve at least a partial response to second-line therapy have a 35-50% chance of long-term survival, whereas those with stable or progressive disease exhibit less favorable outcomes with a median OS of around 3.5 months ([Elstrom et al 2010](#), [van den Neste et al 2016](#)), similar to the expected survival of approximately 4 months for patients left untreated ([Elstrom et al 2010](#), [van den Neste et al 2016](#)).

For patients with relapsed or refractory (r/r) DLBCL and other aggressive B-cell lymphomas with adequate performance status (defined by age and absence of major organ dysfunctions), the European Society for Medical Oncology (ESMO) and NCCN clinical treatment guidelines recommend a salvage regimen with rituximab (R) and platinum-based chemotherapy, followed in **responsive** patients by high-dose chemotherapy and autologous hematopoietic stem cell

transplant (HSCT) (Tilly et al 2015, NCCN v15 2019). The most frequently used salvage regimens for these patients include R-DHAP (R-dexamethasone, cytarabine, cisplatin), R-ICE (R-ifosfamide, carboplatin, etoposide) or R-GDP (R-cisplatin, gemcitabine, dexamethasone) (Tilly et al 2015, NCCN v15 2019). Response rates to these conventional salvage immunochemotherapies is over 60%, including about 30% of complete responses (Coiffier et al 2016). Patients refractory or relapsing within 12 months of first-line therapy have a particularly poor prognosis even with autologous HSCT (Gisselbrecht et al 2010). Without autologous HSCT, chemotherapy provides only short-term disease control in these patients (Elstrom et al 2010).

Three studies are relevant to underline the medical need in patients failing first-line treatment (Table 1-1).

Table 1-1 Phase III trials in relapsed/refractory DLBCL

Trial (N randomized)	CORAL (n=400) ^{3,4}		LY.12 (n=619) ²		ORCHARRD (n=447) ¹	
Treatment Arm	R-ICE	R-DHAP	GDP	DHAP	R-DHAP	O-DHAP
N treated	197	191	303	302	223	222
	%	%	%	%	%	%
ORR in patients who received at least one cycle of salvage therapy regardless of time to relapse/resistance status						
CR + PR	63.5	62.8	46.2	44.7	42.2	37.8
SD	11.7	11.5	5.6	6.0	29.6	28.8
PD	19.3	18.3	25.7	28.8	15.2	17.6
UNK	5.1	7.3	22.5	20.5	13.0	15.8
Completed induction phase with CR/PR/SD	74.7		51.2		69.2	
Patients receiving HSCT, % of all treated	51.3	55	52.1	49.3	37.2	33
Outcome in Refractory and Relapsed within 12 months (early relapsed) from last therapy						
ORR, % in CR/PR (% in R > 12 mo)	46.5 (v. 88%)		35.3 (v. 70%)		29 (v. 67%)	
PFS, %*	23 [£] (% not reported in R>12 mo)		NA		20 (v. 50% in R > 12 mo; HR 0.32, p<0.0001) [#]	
EFS, %*	20 ^{££} (v. 45% in R > 12 mo; p<0.001)		NA		NA	
OS, %*	39 ^{££} (v. 64% in R>12 mo, p<0.001)		NA		30 (v. 60% in R>12mo; HR 0.40, p<0.0001) ^{##}	
Outcome in Refractory and Relapsed within12 months from last therapy with autologous HCT (vs no HSCT)						
PFS, %* / mPFS, mo (vs no HSCT)*	39 / 18.7 (v. 14 / 2.8) [£]		NA		NA / 11.6 (v. NA / 1.4) ^{###}	
OS, %* / mOS, mo (vs no HSCT)*	NA		NA		NA / Not Reached (v. NA / 7.1) ^{###}	

Trial (N randomized)	CORAL (n=400) ^{3,4}	LY.12 (n=619) ²	ORCHARRD (n=447) ¹
NA: not available; R>12: relapsed after 12 months of front line * % of time related parameters by study presented at 3y for CORAL, 2y for ORCHARRD and 4y for LY. 12; £ Data for the 187 patients in CORAL study who received prior rituximab ££ Data for all the patients in CORAL regardless of prior rituximab (n=228 refractory/early relapsed and 160 with late relapse) # median PFS (by BIRC, all pts regardless of arm): refractory/relapsed <12m: 1.5 mo vs R>12: 23.8 mo (Novartis unpublished internal data) ## median OS (all pts regardless of arm): refractory/relapsed <12m: 10.0 mo vs R>12: not reached (Novartis unpublished internal data) ### HSCT: performed in 25.6% of r/r <12m vs 58.9% in R>12 (Novartis unpublished internal data) ¹ van Imhoff et al (2017). ² Crump et al (2014), ³ Gisselbrecht et al (2010), ⁴ van den Neste et al (2016).			

The ‘Collaborative Trial in Relapsed Aggressive Lymphoma’ (CORAL) study demonstrated that approximately 60% of patients with r/r DLBCL respond to second-line salvage immunochemotherapy (R-ICE or R-DHAP), and around 50% of patients receiving this salvage therapy can further receive HSCT ([Gisselbrecht et al 2010](#)) ([Table 1-1](#)). Data from this trial also showed that patients refractory or relapsing within 12 months of rituximab-containing first-line therapy had a particularly poor prognosis, with only 14% of patients not undergoing autologous HSCT being event free at 3 years (median progression free survival (mPFS) in these patients only 2.8 months). On the other hand, for refractory or early relapsing patients undergoing autologous HSCT, the 3-year PFS rate was 39% (and median PFS 18.7 months), highlighting the importance of autologous HSCT as treatment option in this patient population. Response rate was also lower in patients who were refractory or relapsing within 12 months of front line therapy (46.5% vs 87.5% in patients relapsing after 12 months of front line therapy). Another important finding from this trial is that patients not undergoing autologous HSCT can still be rescued and eventually transplanted with further chemotherapy ([Gisselbrecht et al 2010](#), [van den Neste et al 2016](#)), data not shown in [Table 1-1](#). Interestingly, 39% of patients not undergoing transplant after first salvage therapy (i.e., R-ICE or R-DHAP) responded after a second salvage therapy. Indeed, 31% of all patients receiving second salvage were eventually transplanted (87.5% auto / 12.5% allo) and 88% of these transplanted patients were alive at 1 year (median OS not reached at the time of the analysis). On the other hand, patients with SD or PD after initial salvage therapy not responding to second salvage therapy have a dismal prognosis, with a median OS of only 3.4 months ([van den Neste et al \(2016\)](#), data not shown in [Table 1-1](#)) which highlights the need of developing new therapies for these patients.

The National Cancer Institute of Canada Clinical Trials Group (NCIC-CTG) LY.12 trial compared the efficacy GDP versus DHAP and subsequent consolidation by high dose chemotherapy/autologous HSCT in 619 patients with relapsed/refractory aggressive NHL (DLBCL, peripheral T cell lymphoma, and anaplastic large cell lymphoma were enrolled in this trial) ([Crump et al 2014](#)). As observed in CORAL trial, response rate was lower in patients who were refractory or had relapsed within 12 months from initial therapy (35.3% vs 70% in patients relapsing after 12 months of front line therapy) ([Table 1-1](#)). Outcome in patients refractory and relapsed within 12 months from last therapy according to HSCT are not available for this trial.

The short term nature of disease control in many patients with r/r DLBCL and poor prognosis of early relapses was also confirmed in the ORCHARRD trial, which compared the anti-CD20 directed antibody ofatumumab (O) plus DHAP versus rituximab (R) plus DHAP followed by autologous HSCT in patients with r/r DLBCL after first-line treatment ([van Imhoff et al 2017](#)).

All patients enrolled in this trial were refractory to or had relapsed following first-line treatment with rituximab and an anthracycline-based chemotherapy regimen and therefore, this study might represent the most relevant efficacy data of salvage therapy in the rituximab era. Of the 447 randomized patients, 71% were refractory or early relapsed (i.e., did not achieve CR, progressed or experience response for < 12 months) after front line R-CHOP. As was seen in CORAL and LY.12 trials, these patients with refractory or early relapsed disease had a worse outcome when compared with patients relapsing after 12 months of initial therapy [ORR: 29% vs 67%, 2-year PFS: 20% vs 50% (HR 0.32, $p < 0.0001$) and 2-year OS: 30% vs 60% (HR 0.40, $p < 0.0001$)]. As expected, median PFS and OS values were also significantly higher in patients with late relapse (1.5 vs 23.8 months for PFS and 10.0 vs not reached for OS in refractory/early relapsed vs late relapsed patients). HSCT in this group of patients also increased the median PFS and OS when compared with the patients not able to be transplanted (median PFS in transplanted 11.6 months vs 1.4 months in non-transplanted; median OS in transplanted not reached vs 7.1 months in non-transplanted patients) (Table 1-1). These data confirm the poor prognosis of refractory and early relapsing patients after front line therapy and the unmet need for this patient population.

The SCHOLAR-1 meta-analysis (n=636) has reported on the very poor outcome of patients with DLBCL refractory to anti-CD20 monoclonal antibody- and anthracycline-containing regimens (Crump et al 2017). In this meta-analysis, both the ORR and the OS were quite similar regardless of the number of prior lines and the refractory group (refractory after first line vs \geq second line vs relapse within 1 year of autologous HSCT): i) for ORR: 20 vs 26 vs 34%; ii) for median OS: 7.1 vs 6.1 vs 6.2 months.

Concerning r/r FL3B and other aggressive B-cell lymphomas, these patients are also treated according to the DLBCL treatment algorithm and in particular the FL3B subtype is regarded as aggressive lymphoma, with a clinical behaviour very similar to DLBCL and with frequent histological transformation into DLBCL (Dreyling et al 2016, NCCN V15 2019). Indeed, this aggressive FL3B subtype is generally excluded from clinical trials exploring new therapies (e.g., obinutuzumab, idelalisib) for indolent NHL (Sehn et al 2015, Sehn et al 2016, Gopal et al 2014).

In summary, after failure of rituximab containing first line therapy several chemotherapy salvage options are available but none of them seems to be superior from the others. Although all current treatment options have not been compared in a randomized setting, the observed results are quite consistent regardless of the line of therapy and particularly poor in the group of patients with refractory disease and early relapse (i.e., within 12 months of last therapy). This is as well supported by the recent SCHOLAR-1 meta-analysis, showing that the DLBCL population has homogeneous and consistently poor outcomes regardless of refractory group, line of therapy and disease stage (Crump et al 2017).

In conclusion, refractory and early relapsed aggressive B-cell NHL represents a significant unmet medical need and thus novel therapies are urgently needed for this patient population.

1.1.2 Historical experience with viral gene therapies

Retroviral vectors are highly effective gene delivery vehicles for inserting foreign genetic material into the host cell.

Lentiviral vectors, a major subset of retroviral vectors, demonstrate distinct integration patterns compared to other retroviral vectors, which have been predominantly used to date for gene transfer studies. The integration pattern of lentiviral vectors tends to be inside active transcription units as opposed to upstream in the locus control region, where the insertion would have a greater chance of up-regulating gene expression. In addition, lentiviral vectors have no enhancer activity in their long terminal repeat (LTR) regions and have lower levels of poly-A read-through. These are all factors, which improve gene transfer safety (Zaiss et al 2002). Thus, lentiviral vectors appear a safer alternative to retroviral vectors, which is supported by animal models (Montini et al 2006). Lentiviral vector trials have demonstrated in general more polyclonal patterns of vector insertion (Cartier et al 2009, Biffi et al 2013). Importantly, despite a very high transduction efficiency achieved using lentiviral vectors, molecular clonality studies have not indicated any reasons for concern, to date, in published clinical trials (Schambach et al 2013).

For further information refer to the [tisagenlecleucel Investigator's Brochure].

1.1.3 Overview of tisagenlecleucel

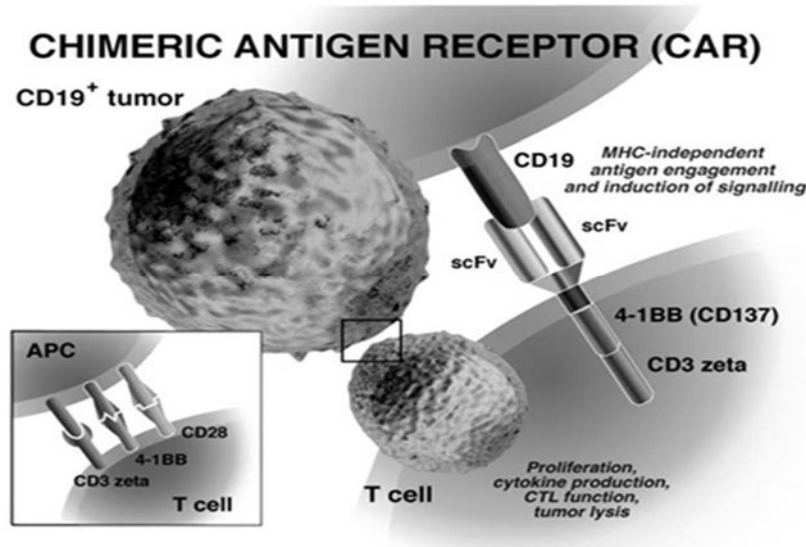
Adoptive T cell therapy for cancer involves the infusion of native or genetically modified mature T cells that have the capacity to recognize and possibly eliminate the patient's malignant cells. In particular, chimeric antigen receptor (CAR)-based approach involves engineering T cells with sequences that encode antibody-based antigen recognition moieties linked to signaling domains. CAR-T cells specifically target and destroy tumor cells in a Major Histocompatibility Complex (MHC) independent manner (Mellman et al 2011).

A promising target antigen for B cell malignancies is CD19, a cell-surface protein whose expression is restricted to B cells and their precursors (Sadelain et al 2003, Porter et al 2011), with no expression on hematopoietic stem cells or non-B cell tissues. CAR-T cells targeting CD19 have been developed to target B cell malignancies.

First generation CARs contain the T cell receptor (TCR) activation signal domain consisting of TCR ζ . Second generation CARs contain costimulatory signaling domains as well: either CD28 or 4-1BB. The 3rd generation CARs contain further advancements such as double costimulatory modules comprised of CD28, 4-1BB plus TCR ζ (June 2007, June et al 2009, Kohn et al 2011).

Tisagenlecleucel (CART-19, CTL019) is a second generation CAR-T cell product that uses autologous peripheral blood T cells that have been genetically modified *ex vivo* to target CD19 on the surface of B cells. As shown in Figure 1-1, the CAR approach uses lymphocytes genetically programmed to express chimeric receptor genes to combine the effector functions of T lymphocytes with the ability of antibodies to recognize predefined surface antigens with high specificity in a non-MHC restricted manner (Gross et al 1989, Pinthus et al 2003). These receptors have the ability to recognize intact membrane proteins independent of antigen processing. The tumor antigen-binding function of CAR is usually accomplished by the inclusion of a single chain variable fragment (scFv) antibody, containing the heavy chain variable domain (V_H) and light chain variable domain (V_L) joined by a peptide linker of about 15 residues in length (Mullaney and Pallavicini 2001).

Figure 1-1 Tisagenlecleucel chimeric antigen receptor design



Recent clinical trials of tisagenlecleucel in r/r CLL, r/r ALL, and r/r B-cell lymphomas have shown promising and durable anti-tumor efficacy ([Porter et al 2011](#), [Grupp et al 2013](#), [Maude et al 2014](#), [Schuster et al 2017](#)). Consequently, tisagenlecleucel appears to be a therapeutic alternative for patients with B cell malignancies (including DLBCL) refractory to the current therapies. For further information refer to the [Tisagenlecleucel Investigator's Brochure].

1.1.3.1 Non-clinical experience

Extensive literature supports the use of engineered T cells for tumor immunotherapy in rodent tumor models ([Calogero et al 2000](#), [Clay et al 2002](#), [Hombach et al 2002](#), [Pule et al 2003](#), [Sadelain 2003](#)). The incorporation of costimulatory signaling modules such as CD28 and 4-1BB in second generation CARs increases potency of the engineered T cells in pre-clinical studies ([Finney et al 1998](#), [Krause et al 1998](#), [Eshhar et al 2001](#), [Maher et al 2002](#), [Finney et al 2004](#), [Friedmann-Morvinski et al 2005](#), [Brentjens et al 2010](#)). The pre-clinical data supporting CAR T cell persistence, expansion and anti-tumor efficacy have been published ([Gross and Eshhar 1992](#), [Milone et al 2009](#)).

1.1.3.2 Clinical experience

Tisagenlecleucel is investigated in several malignancies including r/r ALL, r/r diffuse large B-cell lymphoma (DLBCL), r/r CLL, and follicular lymphoma (FL). Available data show encouraging anti-tumor efficacy with manageable toxicity ([Grupp et al 2013](#), [Porter et al 2011](#), [Schuster et al 2017](#), [Chong et al 2016](#), [Maude et al 2018](#)).

For more details please refer to the [Tisagenlecleucel Investigator's Brochure].

1.1.3.2.1 Cellular kinetics

In adult r/r DLBCL patients from Study C2201, tisagenlecleucel typically exhibits an initial rapid expansion phase, achieving maximal expansion around Day 9 (D9), followed by a bi-exponential decline. The persistence of tisagenlecleucel transgene in peripheral blood has been

observed for up to 2 years ([Schuster et al 2017](#)). All responding patients demonstrated expansion of transgene levels. No clinically relevant impact of patient characteristics and prior therapy on expansion were observed. Moreover, cellular and humoral immunogenicity had no impact on the cellular kinetics or clinical outcome ([Awasthi et al 2017](#)).

In adults with DLBCL or FL in study A2101J, median peak tisagenlecleucel expansion in blood occurred at 8 and 10 days after infusion in responders and non-responders, respectively. No difference was noted between peak CD8-tisagenlecleucel and peak CD4-tisagenlecleucel expansion in responders and non-responders. Among 16 patients in CR (including both DLBCL and FL), 14 had consistently detectable tisagenlecleucel DNA at 6 to 24 months post tisagenlecleucel infusion. Two DLBCL patients lost detectable tisagenlecleucel DNA, one at 3 months and one at 4 months, yet both continue in complete response at 23 and 29 months, respectively.

1.1.3.3 Clinical Efficacy

Two clinical trials with tisagenlecleucel in DLBCL patients failing or not being candidates to HSCT are ongoing with available data:

CTL019A2101J (NCT02030834) ([Schuster et al 2017](#)): this is a single-arm, single-institution trial ongoing at University of Pennsylvania. Patients with CD19+ DLBCL or FL with no curative treatment options, who relapsed, or had residual disease after HSCT, or were not eligible for autologous or allogeneic HSCT, were eligible for the trial. Patients had to have partial response or stable disease to most recent therapy. The 6-month ORR in DLBCL patients was 50% (7/14 patients), with CR achieved in 6 patients (43%; 95% CI: 18-71%). Sustained remissions were achieved, and at a median follow-up of 28.6 months, 86% of patients with DLBCL who had a response (95% CI, 33 to 98) had maintained the response.

CTL019C2201 (NCT02445248) (**JULIET trial**): In Study C2201 (adult patients with r/r DLBCL), the overall response rate (ORR) was 52% (40% CR and 12% PR), and 65% of the patients were relapse-free at 12 months of follow up. Median response duration has not been reached. Most CR patients remained in CR at 3 months ([Schuster et al 2018](#)).

1.1.3.4 Clinical Safety

[Section 4.5](#) outlines identified and potential safety risks of tisagenlecleucel, most of which occur within 8 weeks of infusion.

Safety in adult r/r B-NHL

In study C2201, among the 111 patients assessed for safety, within the first 8 weeks after infusion there were 58% with cytokine release syndrome (CRS) (14% Grade 3, 8% Grade 4), 21% with neurological events (7% Grade 3, 5% Grade 4), and 34% with infections (18% Grade 3, 2% grade 4). The median time to CRS onset was 3 days (range 1-51 days), median CRS duration was 7 days (range 2-30 days); 14% of patients required tocilizumab and 10% of patients required both tocilizumab and corticosteroids. Three patients died within 30 days of tisagenlecleucel infusion. No deaths after infusion were attributed to tisagenlecleucel by the investigators ([Schuster et al 2018](#)).

In study A2101J, 28 patients (14 with DLBCL and 14 with FL) were treated with tisagenlecleucel. Sixteen (57%) patients developed CRS (18% Grade 3-4) and 11 (39%) patients developed neurotoxicity (11% Grade 3-4). There was one death (possibly related to tisagenlecleucel) in a patient with FL, who died 234 days after tisagenlecleucel infusion in pathological CR ([Schuster et al 2017](#)).

For further information refer to the [Tisagenlecleucel Investigator's Brochure].

1.2 Purpose

Despite the fact that most patients with aggressive B-cell NHL, can be cured with conventional frontline immunochemotherapy (e.g., R-CHOP), around one-third of patients will not respond (i.e., will not achieve a CR or PR) or will relapse or progress after front-line treatment. More than half of all these treatment failures include patients not responding (refractory) or relapsing/progressing within a year after the standard frontline immunotherapy (defined as “early relapses”). These patients have a poor prognosis, particularly if they do not respond to further salvage immunochemotherapy or are not eligible for HSCT ([Sarkozy et al 2015](#), [Coiffier et al 2016](#), [Friedberg 2011](#), [Elstrom et al 2010](#)). Novel therapies for refractory and early relapsed DLBCL patients are thus urgently needed.

Given the activity of tisagenlecleucel in DLBCL patients after two or more prior therapies, this phase III trial aims at providing randomized assessment of the safety and efficacy of the treatment strategy with this novel agent against the current standard of care treatment strategy, with the potential to provide additional treatment options for this patient population.

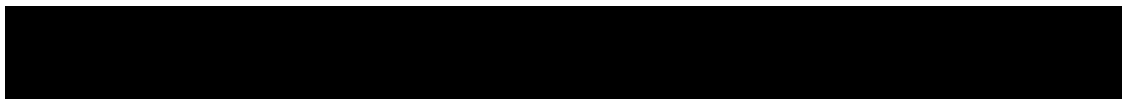


2 Objectives and endpoints

Table 2-1 Objectives and related endpoints

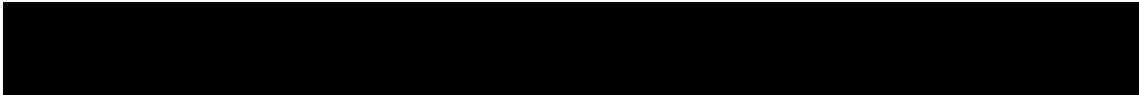
Objectives	Endpoints
Primary Objective	
To compare tisagenlecleucel treatment strategy to SOC treatment strategy with respect to delaying the composite event of disease progression / stable disease at or after the week 12 assessment; or death at any time.	<ul style="list-style-type: none"> EFS, defined as time from date of randomization to the date of first documented disease progression or stable disease at or after the week 12 (± 1 week) assessment, as assessed by blinded independent review committee (BIRC) per Lugano criteria, or death at any time
Secondary Objectives	
<ul style="list-style-type: none"> To compare tisagenlecleucel treatment strategy to SOC treatment strategy with respect to EFS as assessed by local investigator. 	<ul style="list-style-type: none"> EFS as assessed by local investigator
<ul style="list-style-type: none"> To compare tisagenlecleucel treatment strategy to SOC treatment strategy with respect to overall survival (OS). 	<ul style="list-style-type: none"> OS: defined as the time from randomization to date of death
<ul style="list-style-type: none"> To compare tisagenlecleucel treatment strategy to SOC treatment strategy with respect to overall response rate (ORR) To evaluate duration of response (DOR) by BIRC and local investigator. To compare tisagenlecleucel treatment strategy and SOC treatment strategy with respect to time to response (TTR) 	<p>The following endpoints will be evaluated by BIRC and investigator assessment per Lugano criteria:</p> <ul style="list-style-type: none"> ORR: overall response rate as per the Lugano criteria Duration of response: time from the date of first documented response of CR or PR to the date of first documented progression (SD or PD at or after the week 12 (± 1w) assessment will be considered progression) or death due to aggressive B-cell NHL TTR: time from the date of randomization to the date of a patient first achieved a response of CR or PR on or after the Week 12 assessment
<ul style="list-style-type: none"> To evaluate safety and tolerability of tisagenlecleucel treatment strategy versus SOC treatment strategy 	<ul style="list-style-type: none"> Type, frequency and severity of serious and non-serious adverse events and laboratory abnormalities and discontinuations due to adverse events
<ul style="list-style-type: none"> To compare patient reported outcomes (PRO) of health-related quality of life (HRQoL) in both treatment arms. 	<ul style="list-style-type: none"> Time to definitive deterioration in SF-36v2, FACT-Lym, and EQ-VAS

<ul style="list-style-type: none"> Evaluate efficacy and safety of both treatment arms in histological subgroups (e.g. DLBCL, NOS, FL3B, other) and molecular subgroups (e.g. GCB, ABC, other) 	<ul style="list-style-type: none"> EFS, OS and AE
<ul style="list-style-type: none"> To characterize the in vivo cellular kinetics of tisagenlecleucel transduced cells into target tissues (blood, bone marrow, cerebral spinal fluid and other tissues if available), as measured by qPCR summarized by clinical response in patients receiving tisagenlecleucel therapy in arm A or after crossover 	<ul style="list-style-type: none"> Summary of qPCR detected tisagenlecleucel transgene concentrations in peripheral blood and bone marrow (and other tissue, if available), and cellular kinetic parameters from peripheral blood profile samples by time point and clinical response status
<ul style="list-style-type: none"> To characterize the incidence and prevalence of tisagenlecleucel immunogenicity (humoral and cellular) and impact on cellular kinetics, efficacy, and safety in patients receiving tisagenlecleucel therapy in arm A or after crossover 	<ul style="list-style-type: none"> Summary of pre-existing and treatment induced immunogenicity (cellular and humoral) of tisagenlecleucel Levels of pre-existing and treatment induced immunogenicity. Cellular kinetic parameters, concentration-time profile by immunogenicity category (positive/negative), and efficacy (Month 3 response)
<ul style="list-style-type: none"> To assess presence of RCL in patients receiving tisagenlecleucel in arm A or after crossover 	<ul style="list-style-type: none"> RCL by VSV-qPCR
Exploratory Objective(s)*	
<ul style="list-style-type: none"> Characterize the in vivo cellular kinetics (levels or surface expression) of tisagenlecleucel transduced cells in peripheral blood and to target tissues if available as measured from flow cytometry data, in patients receiving tisagenlecleucel therapy in Arm A or after crossover 	<ul style="list-style-type: none"> Summary of surface expression in peripheral blood, bone marrow as appropriate, by time point
<ul style="list-style-type: none"> Characterize and summarize cellular kinetics by use of tocilizumab and also by CRS grade in patients receiving tisagenlecleucel therapy in arm A or after crossover 	<ul style="list-style-type: none"> Cmax, Tmax, AUCs, and other cellular kinetic parameters, use of tocilizumab (YES/NO), and CRS grade
<ul style="list-style-type: none"> To explore the relationship between tisagenlecleucel cellular kinetics, dose, and clinical response (including efficacy and safety) in patients receiving tisagenlecleucel therapy in arm A or after crossover 	<ul style="list-style-type: none"> Parameters: Cmax, Tmax, AUCs, others as appropriate and clinical response parameters (e.g. ORR, DOR, dose)
<ul style="list-style-type: none"> Explore relationship in baseline tumor biopsy specimens between CD19, PD1 and PD-L1 expression, and clinical response in Arm A or after crossover 	<ul style="list-style-type: none"> ORR, DOR, EFS, CD19 expression, PD-1, PD-L1 expression
<ul style="list-style-type: none"> Profile blood soluble markers (e.g. IL-6, gamma interferon) and their correlation with safety and efficacy in Arm A or after crossover 	<ul style="list-style-type: none"> ORR, DOR, EFS and OS, Concentrations of soluble factors in blood, CRS grade and neuronal toxicity
<ul style="list-style-type: none"> Characterize B cell levels over time in both treatment arms and relationship with transgene persistence, clinical response in patients receiving tisagenlecleucel therapy in arm A or after crossover 	<ul style="list-style-type: none"> B cell levels, cellular kinetics, and clinical response
<ul style="list-style-type: none"> Describe the composition of T cell subsets (immunophenotyping in peripheral blood), summarized by clinical response in Arm A or after crossover 	<ul style="list-style-type: none"> ORR, DOR, EFS and OS, CTL019-positive/CD3-positive/CD4-positive and CTL019-positive/CD3-positive/CD8-positive T cells and other leukocyte subsets



-
- | | |
|--|------------------------|
| • Evaluate tisagenlecleucel efficacy in double-hit/triple hit lymphoma patients (Bcl-2, bcl-6 and c-myc expression) in both treatment arms | • ORR, DOR, EFS and OS |
|--|------------------------|
-
- | | |
|--|---|
| • To assess health care resource utilization (HCRU) with respect to hospitalization (i.e. length of stay, frequency), outpatient visit (i.e. frequency), and concomitant medication use for selected adverse events (eg, CRS and Neurological events) in both treatment arms | • HCRU with respect to hospitalization, outpatient visits, and concomitant medication use for selected adverse events |
|--|---|
-

* For patients enrolled in China: please refer to section 8.5.2 and section 8.5.3 for specifics on exploratory assessments.



3 Study design

This is a randomized, open label, multicenter phase III trial comparing the efficacy, safety, and tolerability of tisagenlecleucel treatment strategy to SOC treatment strategy in adult patients with aggressive B-cell NHL after failure of rituximab and anthracycline containing first line immunochemotherapy. Failure of frontline therapy is defined as refractoriness (lack of complete response or progression during therapy) or relapse/progression within 365 days of last dose of first line therapy (in patients who achieved CR on first line therapy).

Following achievement of global study main cohort recruitment target of 318 participants, the recruitment will continue only in China mainland, independently from the global study main cohort, if the number of participants from China mainland randomized in the global study main cohort is not sufficient to support registration in China (at least 36 Chinese mainland patients to be randomized in total). The extension study will follow the same study design as the global study, with the exception that stratification by region will not be applicable (see [Figure 3-1](#)).

Screened patients may undergo non-mobilized leukapheresis for autologous T cell collection after obtaining informed consent (unless historical product is to be used). During the screening period, no lymphoma-specific therapy is allowed prior to randomization. During randomization, patients will be stratified by:

- (a) remission duration (refractory or relapsed < 6 months from last dose of first line therapy vs. relapsed 6 - 12 months inclusive)
- (b) international prognostic index (IPI) score (<2 versus ≥ 2) based on central labs and as per treating physician's assessment at study entry, [The International Non-Hodgkin's Lymphoma Prognostic Factors Project \(1993\)](#), [Moskowitz \(1999\)](#)
- (c) Region (North America vs. Rest of World)

Eligible patients will be randomized into:

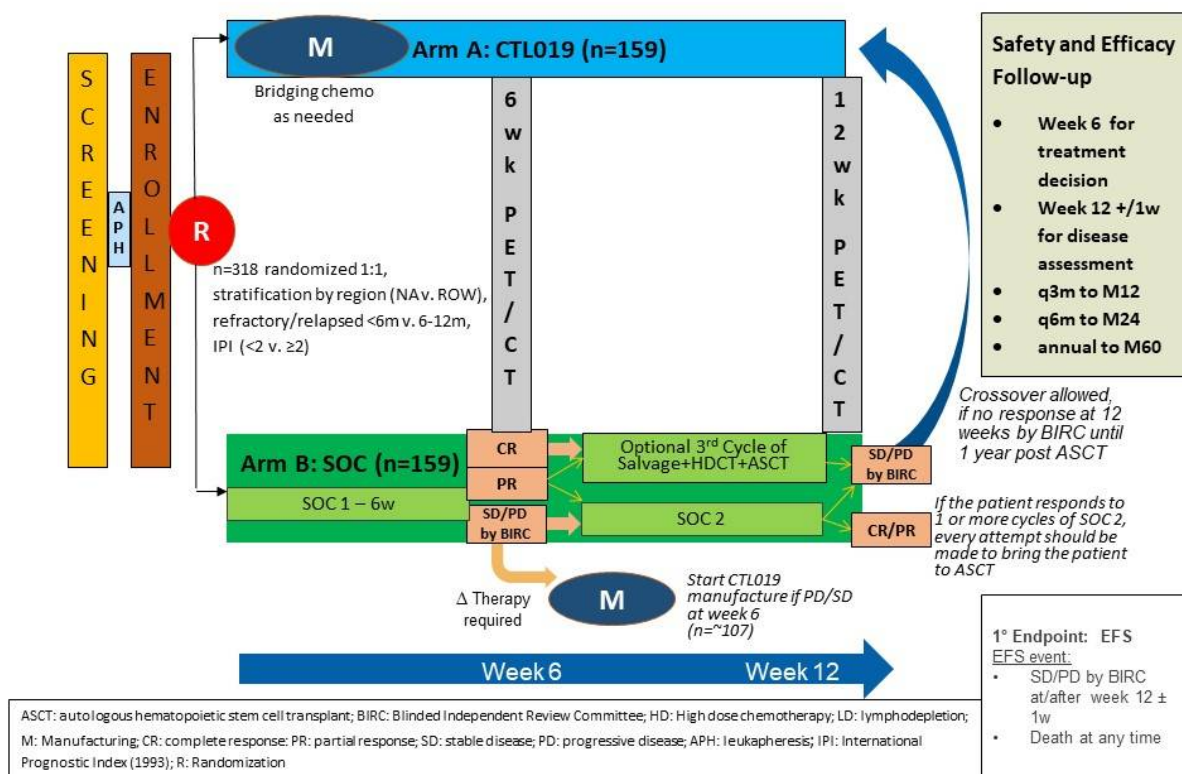
Arm A (tisagenlecleucel treatment strategy, tisagenlecleucel after optional bridging chemotherapy and LD chemotherapy): Patients will receive lymphodepletion chemotherapy (unless the patient has a significant cytopenia, see [Section 6.1.4.2](#)) followed by infusion of tisagenlecleucel. Use of platinum-based bridging chemotherapy (regimens include R-ICE, R-GDP, R-DHAP, or R-GemOx, and can be adjusted as per local practice, see [Section 6.1.1](#)) after randomization and prior to starting lymphodepletion therapy is allowed.

Arm B (standard of care treatment strategy, standard of care chemotherapy followed by transplant): Patients will receive platinum-based immunochemotherapy, followed in responding patients by HDCT and autologous HSCT. Every effort should be made to perform autologous HSCT in patients achieving a PR, if deemed in the patient's best interest by the treating physician. Cells collected as part of the leukapheresis procedure cannot be used for stem cell transplant. A separate collection of cells will be needed if a patient proceeds to autologous HSCT. Patients with response that is not sufficient to allow HSCT should change therapy to one of the other immunochemotherapy regimens listed above at the investigator's discretion in an attempt to achieve a sufficient response and then proceed to HSCT. Only patients who are deemed no longer eligible for HSCT (e.g. adverse event, poor tolerance to immunochemotherapy, worsening of performance status) after two cycles of

immunochemotherapy may proceed to lenalidomide or ibrutinib treatment at investigator discretion. If the assessment of SD or PD is confirmed by BIRC at Week 6, the investigator may request manufacturing of tisagenlecleucel (but not crossover). After receiving 12 weeks of SOC therapy, patients with PR FDG+ disease, SD or PD per local assessment may request manufacturing of tisagenlecleucel. Crossover can only occur following confirmation of SD/PD per BIRC at or after the Week 12 (± 1 week) visit, until 1 year after autologous HSCT as detailed in [Section 8.3.3](#).

Tumor and response assessments will be performed during the screening period (baseline within 2 weeks of randomization), 6 weeks after randomization (± 2 weeks), 12 weeks after randomization (± 1 week), 6 months after randomization (± 2 weeks), every 3 months thereafter (± 2 weeks) for the first year, every 6 months (± 2 weeks) for the second year, and annually thereafter (± 2 weeks) up to 5 years after randomization. All patients who have stable disease/disease progression determined by the local investigator at any time per Lugano classification 2014 require an expedited central tumor response review by the BIRC.

Figure 3-1 Global Study design*



* The China extension cohort will follow the same study design

4 Rationale

4.1 Rationale for study design

This is a randomized, open label, multicenter phase III trial to determine the efficacy and safety of tisagenlecleucel treatment strategy in adult patients with r/r aggressive B-cell NHL after failure of rituximab and anthracycline containing frontline immunochemotherapy.

The outcome of patients with refractory/early relapsed DLBCL treated with first salvage therapy is poor, particularly for those who do not respond to the salvage therapy, who have a median life expectancy of only 4 months ([Elstrom et al 2010](#), [van den Neste et al 2016](#), [Friedberg 2011](#)). As shown by the SCHOLAR-1 meta-analysis ([Crump et al 2016](#)), patients with chemorefractory DLBCL have consistently poor outcomes, regardless of line of therapy, with a median survival of approximately 6 months. In the ORCHARRD trial the median OS of patients who entered the study with chemorefractory disease was around 10 months, significantly shorter than the median OS of patients enrolled with chemosensitive disease. These data support exploring the use of novel therapies in refractory/early relapsed DLBCL patients ([Van Imhoff et al 2017](#)).

Event-free survival is an acceptable primary efficacy endpoint in the setting of aggressive diseases like DLBCL and has shown to be a robust surrogate endpoint for OS in frontline DLBCL trials evaluating immunochemotherapy ([Shi et al 2016](#), [Lee et al 2011](#)). In this trial, EFS is defined as the time from date of randomization to death due to any cause for all patients or lack of response (i.e. PD or SD) at or after the week 12 (± 1 w) assessment.

SD is considered as treatment failure in aggressive B-cell lymphoma and, as demonstrated by the analysis performed in the CORAL study in patients not responding to first and second salvage therapies (and eventually not receiving HDCT and HSCT), the expected survival is only 3.4 months from the start of the second salvage therapy. The ORCHARRD study also showed that only 33% and 37% of patients in the two treatment groups (R-DHAP and O-DHAP respectively) were able to undergo stem cell transplant ([van Imhoff et al 2017](#)). The current goal of salvage therapy in r/r aggressive B-cell lymphoma patients after front line immunochemotherapy is to achieve a good quality response and perform HDCT and HSCT. As a general rule, if a response is not observed after 2-3 cycles of a first salvage therapy, the recommendation is to change to a new salvage therapy (2nd salvage) with the same objective of achieving a response and eventually perform HSCT. If no response is observed, treatment guidelines recommend use of axicabtagene ciloleucel or tisagenlecleucel or another course of 2 cycles of a new salvage therapy (i.e., 3rd salvage), or best supportive care. The possibility of being rescued after 3rd salvage chemotherapy is very low and most patients will die due to quickly progressing disease ([NCCN V15 2019](#), [Van den Neste et al 2017](#)). For this reason, stable disease after 12 weeks (± 1 week) from randomization (which corresponds to approximately 2 rounds of different 2-cycle salvage therapy post randomization) will be considered as event (for both tisagenlecleucel and SOC arms). Patients enrolled in the SOC arm will be eligible to crossover to tisagenlecleucel after BIRC confirmation of PD or SD at or after the week 12 assessment (± 1 week) up until one year after HSCT, since the majority of relapses would occur within this 1 year timeframe. Additionally, patients with BIRC confirmation of PD or SD at the Week 6 assessment (± 2 weeks) or patients with PR FDG+ disease by local assessment at the Week 12 assessment or after will be able to request a tisagenlecleucel

manufacturing slot for potential crossover. Allowing crossover to tisagenlecleucel will confound the assessment of OS, but will ensure the access to a potentially effective therapy in these patients with poor prognosis. As the primary EFS endpoint will be evaluated by BIRC, crossover will only be allowed after PD or SD at or after the week 12 (± 1 week) assessment is confirmed by BIRC in order to avoid informative censoring.

In addition to the response assessment, three Patient Reported Outcome (PRO) tools, FACT-Lym, SF-36 version 2 and EQ-5D-5L, are proposed for this study as they are considered adequate to support the establishment of clinical benefit for lymphoma patients. FACT-Lym tool will be used to assess disease-specific quality of life. SF-36 v2 will assess general health/quality of life with EQ-5D to assess health utility for the purpose of economic evaluation. Both FACT-Lym and SF-36 v2 have been already used in previous tisagenlecleucel pivotal NHL studies.

Safety will be monitored throughout the trial. Per Health Authority guidelines ([FDA 2006](#), [EMA 2009](#)) for gene therapy products or advanced therapy medicinal products that utilize integrating vectors (e.g., lentiviral vectors), all patients treated with tisagenlecleucel must be monitored for specific toxicities for up to a total of 15 years following infusion, irrespective of their response to tisagenlecleucel. All patients who receive tisagenlecleucel will be monitored in this trial for 5 years, followed by semiannual and annual safety assessments in a separate long-term follow-up protocol (CCTL019A2205B) for an additional ten years to further define the long-term effects of tisagenlecleucel therapy.

4.1.1 Rationale for lymphodepletion

Adoptive immunotherapy strategies may be able to capitalize on homeostatic T cell proliferation ([Dummer et al 2002](#)), a finding that naive T cells begin to proliferate and differentiate into memory-like T cells when the total numbers of naive T cells are reduced below a certain threshold ([Goldrath and Bevan 1999](#), [Surh and Sprent 2000](#)). Host lymphodepletion may enhance the effectiveness of adoptively transferred T cells ([Dummer et al 2002](#)). Homeostatic T cell proliferation can lead to activation of certain immune cell subsets ([King et al 2004](#)), providing a potential mechanism of improved anti-tumor responses. T cells can undergo up to seven rounds of cell division after being deprived of contact with antigen presenting cells ([Kaeche and Ahmed 2001](#), [van Stipdonk et al 2001](#)). Lymphodepletion eliminates regulatory T cells and other competing elements of the immune system that act as “cytokine sinks”, enhancing the availability of cytokines such as IL-7 and IL-15 ([Klebanoff et al 2005](#)). Data indicates that the increased antitumor efficacy of adoptive transfer following host conditioning is more than simply “making room” because the quantitative recovery of adoptively transferred T cells in mice reveals that *in vivo* proliferation following adoptive transfer is identical in mice with or without previous irradiation ([Palmer et al 2004](#)).

Fludarabine with cyclophosphamide has been the most commonly utilized lymphodepleting regimen with CD19 CAR-T cell therapies. It has been demonstrated that addition of fludarabine to cyclophosphamide increases CAR-T cell expansion and persistence and improves disease free survival rates in adult patients with r/r NHL ([Turtle et al 2016](#)).

In previous and ongoing studies (CTL019C2201 and CTL019A2101J) with tisagenlecleucel most of the patients received lymphodepleting therapy with fludarabine and cyclophosphamide and around 20% of DLBCL patients received bendamustine.

4.2 Rationale for dose/regimen and duration of treatment

The recommended tisagenlecleucel dose is a single intravenous (i.v.) infusion of $0.6 - 6.0 \times 10^8$ CAR-positive viable T cells, based on available dose-response, dose-safety, and dose-cellular kinetics analyses performed using the data obtained from r/r DLBCL patients (data cut-off date: 8-Mar-2017) in a Phase II study (CTL019C2201; JULIET). This dose is the approved dose in DLBCL in 3rd or later line in the United States (US), European Union (EU), and several other countries. If bridging chemo therapy prior to tisagenlecleucel infusion is used, duration of treatment should follow local prescribing information. The allowed regimens are outlined in [Section 6.1.1](#) (control drugs). Lymphodepleting chemotherapy should be administered as per [Section 6.1.4.2](#).

Dose-response and dose-exposure: Across the dose range studied, dose and exposure were independent. Additionally, clinically meaningful responses were observed from 0.6 to 6.0×10^8 CAR-positive viable T cells.

Dose-safety: In patients with r/r DLBCL, the probability of any grade neurologic events and time to resolution of cytopenias were not impacted by dose. There was an increase in probability of any grade and grade 3/4 CRS with increasing dose; however, the probability of grade 3/4 CRS was comparable across the dose range of 5.0 to 6.0×10^8 CAR-positive viable T cells. In addition, CRS is generally manageable in the study with the steps outlined in the CRS management algorithm ([Section 6.6.2.1](#)).

Based on the totality of the dose-safety, dose-efficacy, dose-exposure and exposure-response, and considering the positive benefit risk observed across the full range of doses, the following dose specification will be utilized in this study: $0.6 - 6.0 \times 10^8$ CAR-positive viable T cells.

For patients in the control arm, the duration of chemotherapy is determined by response to treatment, tolerability and the treating institution's policies. Investigators should refer to the local label for each drug.

4.3 Rationale for choice of comparator drugs

The ESMO and NCCN clinical treatment guidelines for patients with r/r DLBCL recommend for patients with adequate performance status (defined by age and absence of major organ dysfunctions) a salvage regimen with rituximab and chemotherapy followed in responsive patients by high-dose chemotherapy and autologous HSCT ([Tilly et al 2015](#), [NCCN V15 2019](#)). Without autologous HSCT, chemotherapy provides only short-term disease control in r/r DLBCL ([Elmstrom et al 2010](#)). For patients with r/r DLBCL failing first line treatment the established SOC treatment strategy is salvage therapy followed by autologous HSCT.

In recent years, 4 regimens have been mainly used as salvage therapy in patients with r/r DLBCL eligible for autologous HSCT: R-DHAP, R-ICE, R-GDP ([Tilly et al 2015](#)), and R-GemOx ([Mounier 2013](#)). In the present trial, all patients randomized to SOC therapy will receive one of the above-mentioned 4 regimens as per discretion of the treating physician. For patients randomized to the tisagenlecleucel treatment arm, investigators will have the option of

using one of the four treatments as bridging chemotherapy while the patients' tisagenlecleucel product is manufactured. The decision to use bridging chemotherapy is based on investigator decision in the best interest of the patient. The specific dosing regimens of each of the SOC regimens can be found in [Section 6.1.1](#).

Patients in the SOC arm who are unable to achieve a response to salvage therapy are not eligible to proceed to HSCT. Treatment options in this population include the following, with or without rituximab: bendamustine, GDP, GemOx, or lenalidomide. Additional treatment options are limited and include, ibrutinib (for non-GCB DLBCL), the anti-CD19 CAR-T therapies axicabtagene ciloleucel or tisagenlecleucel, and enrolment in clinical trials of new therapies ([Tilly et al 2015](#), [NCCN V15 2019](#)). In the present trial, patients who do not achieve a response to the second line salvage therapy may switch to another salvage regimen in an attempt to achieve a response which may allow the patient to proceed to autologous HSCT. Only patients who are deemed no longer eligible for HSCT (e.g. adverse event, poor tolerance to immunochemotherapy, worsening of performance status) after two cycles of immunochemotherapy may proceed to lenalidomide or ibrutinib treatment at investigator discretion. Patients who are still unable to achieve response at week 12 have the option to crossover to arm A to receive the anti-CD19 CAR-T therapy tisagenlecleucel.

The use of such regimens and their similarities regarding efficacy in r/r DLBCL are supported by the 3 phase III trials discussed in the background section (i.e., CORAL, NCIC-CTG LY.12 and ORCHARRD)(Refer to [Section 1.1.1](#)).

4.4 Purpose and timing of interim analyses

Not applicable.

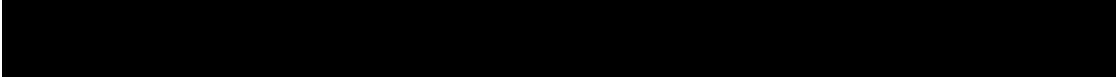
4.5 Risks and benefits

Tisagenlecleucel administered to over 750 patients in clinical trials across the dose ranges tested has a well characterized safety profile in pediatric and young adult patients. Overall, it is anticipated that the study benefits of tisagenlecleucel therapy in this study will outweigh the risks.

Appropriate eligibility criteria and specific dose-limiting toxicity definitions (as applicable) are included in this protocol. Recommended guidelines for prophylactic or supportive management of study-drug induced AEs are provided in [Section 6.6.2](#).

The risk to participants in this trial will be minimized by adherence to the eligibility criteria, close clinical monitoring, and adherence to the recommendations for the management of AEs known to be occur with tisagenlecleucel exposure, periodic review of the safety data by an independent Data Monitoring Committee (DMC), and guidance for the investigators in the [tisagenlecleucel Investigator's Brochure].

Women of child bearing potential (WOCBP) and sexually active males must be informed that receiving the study treatment may pose unknown risks to the fetus if pregnancy were to occur during the study, and agree that in order to participate in the study they must adhere to the contraception requirements outlined in the exclusion criteria. If there is any question that the participant will not reliably comply, they should not be entered or continue in the study ([Section 4.5.3.1](#)).



Safety risks that have been identified with the use of tisagenlecleucel or are considered potentially associated with tisagenlecleucel are briefly outlined below.

4.5.1 Identified safety risks with the use of tisagenlecleucel

Safety risks that have been identified with the use of tisagenlecleucel or are considered potentially associated with tisagenlecleucel are briefly outlined below. For more information, please refer to the [Tisagenlecleucel Investigator's Brochure]

4.5.1.1 Cytokine release syndrome (CRS) / macrophage activation syndrome (MAS)

Cytokine release syndrome (CRS) is an on-target toxicity that is associated with tisagenlecleucel cell expansion, activation and tumor cell killing. It is a result of systemic inflammatory response caused when cytokines such as interferon gamma (IFN γ), interleukin 6 (IL-6) and tumor necrosis factor (TNF) are released by activated T cells or activated monocytes/macrophages. Cytokine release syndrome, including fatal or life-threatening events, has been frequently observed after tisagenlecleucel infusion, in particular if associated with concomitant infections. In almost all cases, development of cytokine release syndrome occurred between 1 to 10 days (median onset 3 days) after tisagenlecleucel infusion. The median time to resolution of cytokine release syndrome was 7 days.

CRS shows a wide range of clinical signs and symptoms ([Table 4-1](#)) and is graded according to the Lee criteria ([Table 4-2](#)) ([Lee et al 2014](#)). In the setting of more severe CRS following CAR T cell therapy, AEs of macrophage activation syndrome (MAS) and hemophagocytic lymphohistiocytosis (HLH) have also been reported. Both HLH and MAS have similar clinical manifestations as CRS, irrespective of the underlying cause, and encompass a group of severe immunological disorders characterized by hyperactivation of macrophages and lymphocytes, proinflammatory cytokine production, lymphohistiocytic tissue infiltration, and immune-mediated multiorgan failure ([Neelapu et al 2018](#)). Patients, who experienced severe CRS, showed a clinical phenotype that resembles MAS or HLH including high fever, multi-organ dysfunction or CNS disturbances that is further evidenced by similar laboratory findings of abnormal macrophage activation, high serum levels of ferritin, lactate dehydrogenase and soluble CD25, low fibrinogen, and cytokine profile. Thus, HLH/MAS might not only belong to a similar spectrum of hyperinflammatory disorders as CRS, but could be interpreted as manifestations of CRS of higher severity ([Teachey et al 2018](#)).

The onset of CRS should be retrospectively defined as the date of the first sign or symptom consistent with CRS. The resolution date of CRS should generally be declared resolved once fever, oxygen, and pressor requirements have resolved. Patients that receive anti-cytokine therapy or antipyretics may quickly resolve fever, however CRS should be considered ongoing even in the absence of fever until improvement of hemodynamic status and/or hypoxia with resolution of pressor and/or oxygen requirements. Concurrent or subsequent neurotoxicity is considered as a separate event (See [Section 4.5.1.2](#)) and does not affect the grading or resolution of CRS. For example, necessity of intubation in those patients having a degree of neurotoxicity (e.g presence of seizure) where there is a concern for their ability to maintain a patent airway should not influence the grading or resolution of CRS ([Lee et al 2019](#)).

Risk factors for severe CRS in pediatric and young adult B-ALL patients are high pre-infusion tumor burden, uncontrolled or accelerating tumor burden following lymphodepleting chemotherapy, active infection and early onset of fever or CRS following tisagenlecleucel infusion.

In pediatric B-cell ALL and adult DLBCL patients, high tumor burden is a risk factor for developing severe CRS.

In the ongoing clinical study B2202 in pediatric and young adult B-cell ALL (N=75), CRS was reported in 77% of patients (47% with Grade 3 or 4). Two deaths occurred within 30 days of tisagenlecleucel infusion: one patient died with CRS and progressive leukaemia and the second patient had resolving CRS with abdominal compartment syndrome, coagulopathy and renal failure when death occurred due to an intracranial haemorrhage. In the ongoing DLBCL clinical study C2201 (N=111), CRS was reported in 58% of patients, (22% with Grade 3 or 4).

Table 4-1 Clinical signs and symptoms associated with CRS
([Lee et al 2014](#))

Organ system	Symptoms
Constitutional	Fever ± rigors, malaise, fatigue, anorexia, myalgia, arthralgia, nausea, vomiting, headache
Skin	Rash
Gastrointestinal	Nausea, vomiting, diarrhea
Respiratory	Tachypnea, hypoxemia
Cardiovascular	Tachycardia, widened pulse pressure, hypotension, increased cardiac output (early), potentially diminished cardiac output (late)
Coagulation	Elevated D-dimer, hypofibrinogenemia ± bleeding
Renal	Azotemia
Hepatic	Transaminitis, hyperbilirubinemia

Table 4-2 Cytokine Release Syndrome Grading
([Lee et al 2014](#))

Grade	Toxicity
Grade 1	Symptoms are not life threatening and require symptomatic treatment only, eg, fever, nausea, fatigue, headache, myalgias, malaise
Grade 2	Symptoms require and respond to moderate intervention Oxygen requirement <40% or Hypotension responsive to fluids or low dose* of one vasopressor or Grade 2 organ toxicity
Grade 3	Symptoms require and respond to aggressive intervention Oxygen requirement ≥40% or Hypotension requiring high dose* or multiple vasopressors or Grade 3 organ toxicity or grade 4 transaminitis
Grade 4	Life-threatening symptoms Requirement for ventilator support or Grade 4 organ toxicity (excluding transaminitis)
Grade 5	Death

*Refer to [Table 6-3](#) for definition of high dose vasopressors

A therapeutic strategy for the management of CRS is provided in [Section 6.6.2.1](#) that should be followed.

4.5.1.2 Neurological events

Neurological events, indicative of encephalopathy and delirium of non-infectious origin, have been observed in patients following various types of T cell directed therapy including tisagenlecleucel and other CAR-T cell therapies of other institutions. The pathophysiology for neurotoxicity is not fully understood but thought to be related to generalized T cell mediated inflammation rather than direct toxicity of CAR-T cells on the brain ([Tey 2014](#)). Some of the neurological events observed may be related to CRS, but whether this results from systemic cytokines crossing the blood brain barrier and engaging cytokine receptors in the brain or from direct cytokine production in the CNS is not clear ([Maus et al 2014](#)). There are no obvious predictors of neurologic toxicity. Confounders, such as preceding or newly induced anti-cancer treatment regimens, might be involved.

Early neurological events are the second most-common adverse reaction associated with CAR-T therapies. In an attempt to standardize the assessment of these events, the CARTOX Working Group has suggested the name CAR T cell-related encephalopathy syndrome (CRES) ([Neelapu et al 2018](#)). This syndrome typically manifests as a toxic encephalopathy with a wide range of variable symptoms such as aphasia, confusion, delirium, tremors, occasionally seizures and rarely life-threatening cerebral edema. The manifestation of CRES is biphasic, with the first phase occurring concurrently with cytokine release syndrome (CRS) symptoms typically within the first 5 days after CAR T cell therapy, and the second phase after CRS subsides. Delayed neurological events with seizures or episodes of confusion 3-4 weeks following CAR T cell therapy have been reported to occur in approximately 10% of patients.

Although encephalopathy is a dominant feature of neurotoxicity following treatment with CAR T cell therapy, there are other neurologic symptoms that should be taken into account. The American Society for Transplantation and Cellular Therapy (ASTCT) recently defined the term Immune effector Cell-Associated Neurotoxicity Syndrome (ICANS) as “a disorder characterized by a pathologic process involving the central nervous system following any immune therapy that results in the activation or engagement of endogenous or infused T cells and/or other immune effector cells. Symptoms or signs can be progressive and may include aphasia, altered level of consciousness, impairment of cognitive skills, motor weakness, seizures, and cerebral edema” ([Lee et al 2019](#)). A grading system was developed in order to characterize this syndrome ([Table 4-3](#)) which incorporates key aspects of the mini-mental status exam via the Immune effector Cell-associated Encephalopathy (ICE) score ([Table 4-4](#))

In clinical trials, the majority of neurological events following tisagenlecleucel infusion were observed within 8 weeks, however, neurological events with later onset > 8 weeks and not in the context of CRS have also been reported. Most neurological events observed within 8 weeks were transient or self-limiting in nature. Frequently, encephalopathy, confusional state and delirium were observed. Other manifestations include a multifarious set of signs and symptoms including seizures, aphasia, speech disorder, and tremor. Some of the events are severe and may have a life-threatening outcome.

Notably, the onset of neurological toxicity can be concurrent with CRS, following resolution of CRS or in the absence of CRS. The incidence appeared to be greater with higher CRS severity and prior history of CNS leukemia and history of other prior CNS diseases. Encephalopathy typically occurred after peak CRS symptoms and tended to be self-limiting with some exceptions. Delayed onset of neurological events may also occur as CRS is resolving or after CRS has completely resolved. In paediatric and young adult B-cell ALL patients, manifestations of encephalopathy and/or delirium occurred in 40% of patients (13% were Grade 3; no grade 4 were observed) within 8 weeks after tisagenlecleucel infusion. In DLBCL patients, manifestations of encephalopathy and/or delirium occurred in 21% of patients (12% were Grade 3 or 4) within 8 weeks after tisagenlecleucel infusion.

The causality assessment of neurological events in patients treated with tisagenlecleucel can be confounded as CNS toxicity may be associated with chemotherapy used for lymphodepletion and the presence of comorbid conditions such as CRS, fever and infections.

Table 4-3 Immune effector Cell-Associated Neurotoxicity Syndrome (ICANS) Grading
([Lee et al 2019](#))

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE Score[^] (Table 4-4)	7-9	3-6	0-2	0 (patient is unarousable and unable to perform ICE)
Depressed level of consciousness^v	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma
Seizure	N/A	N/A	Any clinical seizure focal or generalized that resolves rapidly; or Non-convulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (>5 min); or Repetitive clinical or electrical seizures without return to baseline in between.
Motor findings[§]	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis
Elevated ICP / Cerebral edema	N/A	N/A	Focal/local edema on neuroimaging [#]	Diffuse cerebral edema on neuroimaging; Decerebrate or decorticate posturing; or Cranial nerve VI palsy; or Papilledema; or Cushing's triad

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

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

^v Depressed level of consciousness should be attributable to no other cause (e.g. no sedating medication)

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

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



Table 4-4 Immune effector Cell-associated Encephalopathy (ICE) score
(Lee et al 2019)

Category	Test	Scoring
Orientation	Orientation to year, month, city, hospital	4 points total (1 point each)
Naming	Ability to name 3 objects (e.g. point to clock, pen, button)	3 points total (1 point each)
Following Commands	Ability to follow simple commands (e.g. "Show me 2 fingers" or "Close your eyes and stick out your tongue")	1 point
Writing	Ability to write a standard sentence (e.g. "Our national bird is the bald eagle")	1 point
Attention	Ability to count backwards from 100 by 10	1 point

For the management of neurological events see [Section 6.6.2.2](#).

4.5.1.3 Hypersensitivity including acute infusion reactions

Since tisagenlecleucel is an autologous cellular product, hypersensitivity may occur due to the excipients (such as dimethyl sulfoxide (DMSO) or dextran 40) of the infused solution in which the cells are dispersed. In addition, host immune responses may result from presentation of CAR transgene expressed immunogenic epitopes including murine sequences in the scFv extracellular binding domain (derived from a murine monoclonal antibody) or novel epitopes arising at junctions between components of the CAR fusion polypeptide ([Park et al 2007](#); [Lamers et al 2006](#); [Lamers et al 2007](#); [Lamers et al 2011](#)).

Clinically, hypersensitivity reactions can be classified as 'immediate' or 'delayed' depending on their onset after drug administration ([Corominas et al 2014](#); [Limsuwan and Demoly 2010](#)). In principle, immediate reactions including acute infusion reactions occur within less than 1 hour after drug administration and may present in a wide range of symptoms such as fever, chills, nausea, urticaria, angioedema, rhinitis, conjunctivitis, dyspnea, bronchospasm, tachycardia, hypotension, anaphylaxis or anaphylactic shock. Delayed hypersensitivity reactions appear after more than 1 hour and up to several days after drug exposure and could include variable cutaneous symptoms such as late-occurring urticaria, maculopapular eruptions, fixed drug eruptions, vasculitis, toxic epidermal necrolysis, Stevens- Johnson syndrome, or drug reaction with eosinophilia and systemic symptoms (DRESS) ([Averbeck et al 2007](#); [Descotes 2012](#); [Corominas et al 2014](#)).

To date, the majority of events observed after tisagenlecleucel infusion were mild or moderate in severity, manageable and recovered.

Patients will have typically received lymphodepleting chemotherapy that is completed several days prior to tisagenlecleucel infusion. Therefore it should be kept in mind that symptoms and findings at this time may also be the result of the onset of chemotherapy related toxicities.

A therapeutic strategy for the management of hypersensitivity including acute infusion reactions is provided in [Section 6.6.2.3](#).

4.5.1.4 Tumor lysis syndrome (TLS)

Tumor lysis syndrome (TLS) is a potentially life-threatening metabolic disorder that occurs when tumor cells undergo rapid decomposition spontaneously or in response to cytoreductive

therapy. It tends to occur particularly with highly effective therapies and in patients with high tumor burden and cancers with a high potential for cell lysis include high-grade lymphomas, acute leukemias, and other rapidly proliferating tumors.

Metabolic abnormalities characteristic of TLS include abnormally high serum uric acid levels (hyperuricemia) resulting from the breakdown of purine-containing nucleic acids and major electrolyte imbalances such as hyperkalemia, hyperphosphatemia, and hypocalcemia. Delayed recognition of the metabolic imbalances caused by the massive release of tumor cell contents may result in clinical complications such as acute kidney injury, seizures, and cardiac arrhythmias (Mughal et al 2010).

Tumor lysis syndrome was clinically observed in a timely relation to tisagenlecleucel T cell expansion. In the clinical experience with tisagenlecleucel thus far, most cases of TLS had a grade 3 in Common Terminology Criteria for Adverse Events (CTCAE) severity, however, the risk has been moderate to low with appropriate monitoring after lymphodepleting chemotherapy, prophylaxis and treatment as needed.

A therapeutic strategy for the management of TLS is provided in [Section 6.6.2.4](#).

4.5.1.5 Infections

There is an increased risk and severity of infections in patients with longer and more intense immunosuppression. Patients treated with tisagenlecleucel are at risk of infection for several reasons:

- Underlying bone marrow disease or dysfunction increases the risk of infections.
- Patient with prolonged and profound immunosuppression are at enhanced risk for more frequent and severe opportunistic infections. This may result from preceding anti-cancer treatment, such as radiation or chemotherapy, and lymphodepleting chemotherapy prior to treatment with tisagenlecleucel causing severe neutropenia and/or B-cell depletion from tisagenlecleucel.
- B-cell depletion is known to be associated with hypo- or agammaglobulinemia that contributes to the risk.

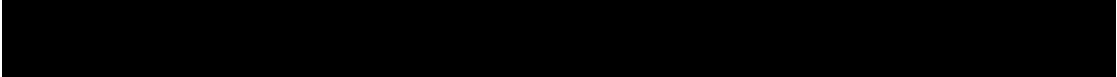
Serious infections were observed in patients after tisagenlecleucel infusion, some of which were life- threatening or fatal.

A therapeutic strategy for the management of infections is provided in [Section 6.6.2.5](#).

4.5.1.5.1 Viral reactivation

Patients with active hepatitis B or prior or active hepatitis C have been excluded from prior clinical studies with tisagenlecleucel, because of the potential risk of viral reactivation and the risk of fulminant hepatitis, hepatic failure and fatal outcome. Human immunodeficiency virus (HIV) positive patients have been also excluded, because of the possible effect on HIV viral suppression.

In addition, there is currently no experience with manufacturing tisagenlecleucel for patients testing positive for active hepatitis B virus (HBV), hepatitis C virus (HCV), and HIV. Patients are to be screened for any active HBV, HCV or HIV infection prior to leukapheresis.



Participants with confirmed active hepatitis B, hepatitis C or HIV will not be enrolled in the study; for detailed exclusion criteria see [Section 5.2](#) for serology assessment see [Section 16.1](#).

4.5.1.6 Febrile neutropenia

Febrile neutropenia and associated events such as grade 3 or grade 4 decreased neutrophil counts with elevated temperature were reported in clinical studies with tisagenlecleucel. The use of chemotherapy is known to be associated with the risk of neutropenia and if severe, with febrile neutropenia. The risk of neutropenia depends on various factors such as type and dose of chemotherapy used, age, gender, performance status and baseline hematology lab data. As lymphodepleting therapy is used in all patients with a white blood cell (WBC) count >1000 cells/ μ L, febrile neutropenia is seen in patients treated with tisagenlecleucel regimen. Also, as lymphodepleting therapy is given close to the infusion of tisagenlecleucel (within two weeks), therefore, overlapping toxicities can be expected.

A therapeutic strategy for the management of febrile neutropenia is provided in [Section 6.6.2.6](#).

4.5.1.7 Prolonged depletion of normal B cells and agammaglobulinemia

Since normal B-cells express CD19, B-cell aplasia is an expected on-target toxicity of a successful CD19-directed CAR T cell therapy and a useful surrogate reflecting the persistence of CAR T cells and effectiveness of treatment. B-cell aplasia has been observed in all responding patients with B-ALL. The AEs observed after tisagenlecleucel infusion were managed well by treatment with immunoglobulins.

Loss of B-cells can result in hypo- to a-gammaglobulinemia, potentially rendering the patients more susceptible to infections, especially with encapsulated organisms; and viral reactivation such as herpes viruses ([Section 4.5.1.5.1](#)).

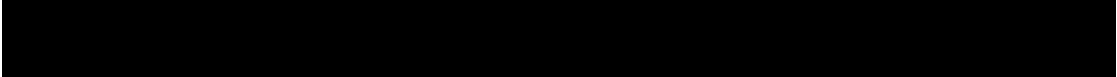
Given that a typical T-lymphocyte may have a lifespan of 40 years, tisagenlecleucel may potentially be detectable in a patient for a very prolonged period and **prolonged** depletion of B-cells may occur, in particular in the subset of patients who continue to demonstrate a tumor response. Long term data are currently not available. A therapeutic strategy for the management of B cell depletion with resulting hypogammaglobulinemia is provided in [Section 6.6.2.7](#).

4.5.1.8 Hematopoietic cytopenias not resolved by day 28 post infusion

Hematopoietic cytopenias are an on-target effect after tisagenlecleucel infusion and activity of tisagenlecleucel on normal B-cells.

Patients treated with tisagenlecleucel may exhibit hematopoietic cytopenias for several weeks an on-target effect after tisagenlecleucel exposure and as sequelae of bridging and lymphodepleting chemotherapy. Prolonged neutropenia has been associated with increased risk of infection. Myeloid growth factors, particularly granulocyte-macrophage colony stimulating factor (GM-CSF), are not recommended during the first 3 weeks after tisagenlecleucel or until CRS has resolved.

A therapeutic strategy for the management of hematopoietic cytopenias is provided in [Section 6.6.2.8](#).



4.5.2 Potential safety risks

Thus far, an association with the potential safety risks briefly described below and tisagenlecleucel have not been confirmed. However, these topics are being closely monitored due to their clinical relevance.

4.5.2.1 Cerebral edema

Five fatal cases of cerebral edema occurred in the ROCKET study in adult ALL treated with JCAR015 and were characterized by a rapid evolution soon after JCAR15 infusion appeared to be resistant to anti-cytokine treatment, and ensued brain death within 1-2 days after diagnosis. Following a retrospective exploratory analysis of these five cases, it is believed that these fatal cerebral edema cases emerged from fast and early CAR-T-cell expansion due to the specific CAR-T construct and subsequent sharp spike in cytokines ([Gilbert 2017](#)).

No fatal cerebral edemas have been reported following tisagenlecleucel infusion in the clinical development program or the post-marketing setting to date that would resemble the clinical course reported for JCAR015. JCAR015 presents a different construct of an anti-CD19 CAR-T-cell product compared to tisagenlecleucel.

4.5.2.2 Replication competent lentivirus (RCL) production

Replication-competent lentivirus (RCL) may be generated during tisagenlecleucel manufacturing using a lentiviral vector to encode anti-CD19 CAR or subsequently after introduction of vector transduced viable T cells into the patient.

However, generation of RCL resulting from manufacturing is highly unlikely since elements are incorporated in the design of the vector system that minimize the probability of recombination and generation of RCL. Furthermore, the vector used to transduce the T cells undergoes sensitive assays for detection of RCL. Thus patients will only receive cell products that meet RCL release criteria considered sufficient to confirm the absence of RCL in tisagenlecleucel and the negligible probability of *de novo* generation of any RCL.

Tisagenlecleucel uses third generation self-inactivating lentiviral vector to safeguard against the potential of generating RCL. None of the participants tested in the tisagenlecleucel development program showed evidence of RCL. However, generation of an RCL following tisagenlecleucel infusion remains a theoretical possibility. The development of RCL could pose a risk to both the patients and their close contact(s), and therefore, monitoring for RCL will be conducted during the course of the trial (see [\[Investigational Product Handling Manual\]](#) for a description of the assays).

As per guidance for gene therapy medicinal products, patients exposed to tisagenlecleucel will be monitored for 15 years following last treatment for vectors persistence and RCL within the long-term follow-up study. In case of suspected secondary malignancies, as per the guidance “Testing of Retroviral Vector-Based Human Gene Therapy Products for Replication Competent Retrovirus During Product Manufacture and Patient Follow-up” biopsy sample of neoplastic tissues or relevant autopsy tissues will be collected for RCL testing ([FDA 2020](#)).

The management of this potential risk is addressed in [Section 6.6.2.9](#).

4.5.2.3 Secondary malignancies (including vector insertion site oligo/monoclonality)

Secondary malignancies in cancer patients, i.e., newly occurring malignancies other than the primary malignancy (e.g., T cell and non-T cell hematological malignancies, solid tumors), can be increased as a result of both previous chemotherapy and radiation therapy exposure and partly due to increased rates within families ([Friedman et al 2010](#)). The rate of new malignancy detection following tisagenlecleucel therapy will need to take into account these additional confounding risk factors.

Transduction of a patient's T cells with the lentiviral vector could lead to insertional mutagenesis resulting in an uncontrolled T cell proliferation and an oncogenic effect that could result in T cell and non-T-cell malignancies.

[Ruella et al \(2018\)](#) reported a B-cell ALL patient treated in an early clinical study at the University of Pennsylvania (Penn) / Children's Hospital of Philadelphia with CTL019 as manufactured by Penn. The patient showed an initial response to treatment and relapsed 9 months after infusion with CD19-negative leukemia cell that aberrantly expressed the anti-CD19 CAR. The CAR gene was unintentionally introduced into a single leukemic B cell during CAR-T cell manufacture at Penn and its product bound in cis to the CD19 epitope on the surface of leukemic cells, masking it from recognition by and conferring resistance to the CAR-T.

The Novartis manufacturing process for tisagenlecleucel is designed to significantly reduce the probability of contaminating B cells in the T cell culture. Therefore, the risk of CAR transduction of B cells as observed at the early CTL019 study at Penn and described in the publication by Ruella et al can be considered low with the current Novartis manufacturing process.

As described in [Section 4.5.2.2](#), tisagenlecleucel uses third generation self-inactivating lentiviral vector to safeguard against the potential oncogenic effects. Insertional mutagenesis was evaluated in two lentivirus insertion site analysis (LISA) studies where 12 batches of manufactured patient product ready for infusion and two batches of product manufactured from healthy donor cells were analyzed. The results indicate that there was no preferential integration near genes of concern, no preferential sites of integration (hot spots), and no preferential outgrowth of cells harboring integration sites of concern.

Tisagenlecleucel is based on autologous, fully differentiated T cells and therefore the carcinogenicity risk is considered to be low in comparison to genetic modification or repair such as HSC. In a recent review of CAR-T cell therapies, ([Bonifant et al 2016](#)) as well as ([Mohanlal et al 2016](#)) discussed that to date no cases of malignant transformation have been reported for genetic modification of T cells and that there currently is no evidence for vector-induced immortalization, clonal expansion, or enrichment for integration sites near genes implicated in growth control or transformation. This is supported by the results of the lentivirus insertion site analysis (LISA) studies performed during the development of tisagenlecleucel.

Theoretically, CAR-positive viable T cells could proliferate without control of normal homeostatic mechanisms. In pre-clinical studies ([Milone et al 2009](#)) and clinical experience to date ([Porter et al 2011](#), [Grupp et al 2013](#), [Maude et al 2014](#)), CAR-positive viable T cells have only proliferated in response to physiologic signals or upon exposure to CD19 antigen. In the

context of tisagenlecleucel therapy, it is expected that the T cells will proliferate in response to signals from the CD19 expressing malignant tumor and normal B cells. This could be either harmful depending on the extent of proliferation or beneficial, since clonal dominance of adoptively transferred T cells has been associated with tumor reduction in adoptive transfer trials ([Dudley et al 2002](#), [Dudley et al 2005](#)).

The management of this potential risk is addressed in [Section 6.6.2.10](#).

4.5.2.4 New occurrence or exacerbation of an autoimmune disease

An emerging number and variety of autoimmune diseases following after anti-cancer treatment including immunotherapy are reported, ranging from asymptomatic immunological alterations to life-threatening systemic autoimmune diseases ([Pérez-De-Lis et al 2017](#)). However, specific etiopathogenic mechanisms that could clearly link the induced autoimmune disorder with the immunological pathways altered by the anti-cancer treatments are not well understood. Persistent immune abnormalities after treatment with chemotherapy, development of auto-antibodies and neoantigens are proposed to be crucial in the pathogenesis of autoimmune diseases post anti-cancer treatment ([Descotes and Gouraud 2008](#), [Chang and Gershwin 2010](#), [Amos et al 2011](#)).

The risk of autoimmune reaction with tisagenlecleucel is low since CD19 is not present on most normal tissue other than normal B-cells. New occurrence or exacerbation of an autoimmune disorder has not been observed with tisagenlecleucel thus far.

No AEs associated with this potential were observed in tisagenlecleucel clinical trials.

4.5.2.5 Hematologic disorders (incl. aplastic anemia and bone marrow failure)

There is potential risk of a hematologic disorder such as aplastic anemia or bone marrow failure, given that tisagenlecleucel is a genetically modified cell product that may have the potential to affect hematopoietic cell function, as could prior chemotherapy and radiation given for the underlying malignancy.

4.5.2.6 Transmission of infections agents

Transmission of infections agents could lead to new infections and reactivation of pre-existing viral disease (e.g., HBV, HCV, or HIV), respectively, in close contacts including personnel involved in the tisagenlecleucel manufacturing process, health care providers involved in leukapheresis and administering tisagenlecleucel or the patients treated with tisagenlecleucel.

Multiple steps are required to produce tisagenlecleucel CAR-T-cells, involving leukapheresis to obtain patient autologous starting material, enrichment and activation, gene transduction via lentiviral vector and expansion. Transmission of infectious material via product could potentially derive from the patient's own leukapheresis material prepared from autologous blood, other material including the tisagenlecleucel viral vector required to manufacture tisagenlecleucel, through contamination during the manufacturing process or inadequate storage. Due to the nature of the product (i.e., cells), there is no possibility to introduce terminal sterilization or dedicated viral removal and inactivation steps. Stringent precautions to prevent introduction of viral adventitious agents and to ensure microbial safety of tisagenlecleucel are

in place in compliance with principles of good manufacturing practices and regulatory guidelines.

The risk associated with tisagenlecleucel is considered low.

4.5.2.7 Decrease in cell viability due to inappropriate handling of the product

Inappropriate handling of the manufactured product including transport, storage in addition to thawing and standing time prior to infusion may result in a decrease of viable cells. This may impact the efficacy and safety of tisagenlecleucel. Qualified center personnel must follow appropriate protocols for product handling to receive, thaw, and infuse the finished tisagenlecleucel product. Please refer to the [\[CTL019 Leukapheresis Cryopreservation and Scheduling Manual for Clinical Trials\]](#).

4.5.3 Other risks

4.5.3.1 Pregnancy, lactation, and effects on fertility

No preclinical reproductive studies have been conducted with tisagenlecleucel to assess whether it can cause fetal harm when administered to a pregnant woman. The human placenta forms an incomplete barrier for blood cells, allowing bidirectional passage of nucleated blood cells. Circulating maternal cells transfer to the fetus during pregnancy, where they may integrate with the fetal immune and organ systems, creating a state of maternal microchimerism (MMc) ([Loubiere et al 2006](#), [Stevens 2016](#)). Hence, there is a potential risk that immunologically active maternal tisagenlecleucel positive T cells may cross the placenta. Currently, the potential impact on the offspring's B cells such as inducing B-cell lymphocytopenia or other potential toxicities such as effects on the development of autoimmune disease is not known.

As it is also not known whether tisagenlecleucel can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity, tisagenlecleucel should not be administered to pregnant women and care should be taken to avoid conceptions.

Therefore, women of child bearing potential (WOCBP), defined as all women physiologically capable of becoming pregnant, and sexually active males are excluded from clinical trials with tisagenlecleucel unless they use adequate contraception. No data are currently available to determine the duration of contraception after receiving tisagenlecleucel.

WOCBP and sexually active males must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study, and agree that in order to participate in the study they must adhere to the contraception requirements outlined in the exclusion criteria. WOCBP and sexually active males who receive tisagenlecleucel must adhere to contraception requirements for at least 12 months following tisagenlecleucel infusion and until CAR T cells are no longer present by qPCR on two consecutive tests. The qPCR test results will be available upon request. For patients who move to long term additional follow-up after tisagenlecleucel infusion please refer to [Table 8-12](#) for unscheduled qPCR collections for the purposes of determining when contraception requirements will end. In addition, male participants must not donate sperm and female patients must not donate oocytes. If there is any question that the participant will not reliably comply, they should not be entered or continue in the study.

There is no information regarding the presence of tisagenlecleucel in human milk, the effect on the breast-fed child or the effects of tisagenlecleucel on milk production. Nursing women are excluded from participation in this study.

4.5.3.2 Risks associated and with standard of care immunochemotherapy

The toxicities of SOC treatment are widely described in [Gisselbrecht et al \(2010\)](#), [Crump et al \(2014\)](#), [Tilly et al \(2015\)](#), [Van den Neste et al \(2016\)](#), [Van Imhoff et al \(2017\)](#), [Van den Neste et al \(2017\)](#). Preventive measures, monitoring and management of toxicities should be managed as per local standard of care and the locally approved labels, including contraception requirements, contraindications, use of concomitant medication, special warnings and precautions.

5 Population

The target population consists of adult participants with aggressive NHL who are refractory or relapsed within 365 days of their last dose of first line immunochemotherapy and eligible for stem cell transplant (SCT). Approximately 318 participants will be randomized for treatment in the global study main cohort. Additional patients may be enrolled in the China extension upon completion of enrollment of the global study main cohort in order to support registration in China. It is planned to randomize at least 36 patients from mainland China (in the global study or/and in the China Extension). It is anticipated that the life expectancy of randomized patients is at least 12 weeks.

The investigator or designee must ensure that only participants who meet all the following inclusion and none of the exclusion criteria at screening are offered treatment in the study. Central lab must be used to confirm eligibility of all lab parameters listed in [Section 5.1](#) and [Section 5.2](#).

5.1 Inclusion criteria

Participants eligible for inclusion in this study must meet **all** of the following criteria:

1. Signed informed consent must be obtained prior to participation in the study.
2. Patients must be ≥ 18 years of age at the time of informed consent form (ICF) signature.
3. Histologically confirmed (by local histopathological assessment), aggressive B-cell NHL at relapse/progression or PR after front line therapy. For patients with relapse/progression, if biopsy after relapse/progression is not available or it is not clinically feasible to obtain a new biopsy, an archival tumor biopsy from the initial diagnosis may be submitted. For patients in PR after at least 6 cycles of first line treatment, a new biopsy must be submitted. (Refer to [Section 8.5.3](#)). Aggressive B-cell NHL is heretofore defined by the following list of subtypes ([Swerdlow et al 2016](#)):
 - DLBCL, NOS
 - FL grade 3B,
 - Primary mediastinal large B cell lymphoma (PMBCL),
 - T cell rich/histiocyte rich large B cell lymphoma (T/HRBCL),
 - DLBCL associated with chronic inflammation,

- Intravascular large B-cell lymphoma,
 - ALK+ large B-cell lymphoma,
 - B-cell lymphoma, unclassifiable, (with features intermediate between DLBCL and classical HL),
 - High grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements,
 - High grade B-cell lymphoma, NOS
 - HHV8+ DLBCL, NOS
 - DLBCL transforming from follicular lymphoma
 - DLBCL transforming from marginal zone lymphoma
 - DLBCL, leg type
4. Relapse or progression within 365 days from last dose of anti-CD20 antibody and anthracycline containing first line immunochemotherapy or refractory (have not achieved a CR).
5. Patient is considered eligible for autologous HSCT as per local investigator assessment.
Note: Intention to transplant and type of HDCT regimen will be documented in the IRT system
6. Disease that is both active on PET scan (defined as Deauville score of 4 or 5) and measurable on CT scan, defined as:
- Nodal lesions >15 mm in the long axis, regardless of the length of the short axis, and/or
 - Extranodal lesions (outside lymph node or nodal mass, but including liver and spleen) >10 mm in long AND short axis
7. ECOG performance status 0 or 1
8. Adequate organ function:
- a. Renal function defined as:
- Serum creatinine of $\leq 1.5 \times \text{ULN}$, OR $\text{eGFR} \geq 60 \text{ mL/min/1.73 m}^2$
- b. Hepatic function defined as:
- $\text{ALT and AST} \leq 5 \times \text{ULN}$
 - Total Bilirubin $\leq 1.5 \times \text{ULN}$ with the exception of patients with Gilbert syndrome who may be included if their total bilirubin is $\leq 3.0 \times \text{ULN}$ and direct bilirubin $\leq 1.5 \times \text{ULN}$
- c. Hematologic Function (regardless of transfusion) defined as:
- Absolute neutrophil count (ANC) $>1000/\text{mm}^3$
 - Platelets $\geq 50,000/\text{mm}^3$
 - Hemoglobin $>8.0 \text{ g/dl}$
- Only for patients with non-historical leukapheresis:
- Absolute lymphocyte count (ALC) $>300/\text{mm}^3$ or
 - Absolute number of CD3+ T cells $>150/\text{mm}^3$
- d. Adequate pulmonary function defined as:
- No or mild dyspnea ($\leq \text{Grade 1}$)

- Oxygen saturation measured by pulse oximetry > 90% on room air
 - Forced expiratory volume in 1 s (FEV1) \geq 50% or carbon monoxide diffusion test (DLCO) \geq 50% of predicted level
9. Must have a leukapheresis material of non-mobilized cells available for manufacturing.
Note: Please refer to [Section 6.2.2](#), [Section 8.1](#) (Leukapheresis) for prohibited concomitant medications and washout times to ensure adequate collection as well as the [\[Investigational Leukapheresis, Cryopreservation, and Scheduling Manual\]](#) for specific collection procedures.

5.2 Exclusion criteria

1. Epstein Barr Virus positive (EBV+) DLBCL, NOS, Richter's transformation, and Burkitt lymphoma, and primary DLBCL of CNS.
2. Prior treatment with anti-CD19 therapy, adoptive T cell therapy, or any prior gene therapy product
3. Treatment with any systemic lymphoma-directed second line anticancer therapy prior to randomization. Only steroids and local irradiation are permitted for disease control.
4. Active CNS involvement by disease under study are excluded, except if the CNS involvement has been effectively treated and local treatment was >4 weeks before randomization
5. Prior allogeneic HSCT
6. Investigational medicinal product (IMP) within the last 30 days prior to screening **Note:** IMPs should not be used at any time while on study until the first progression following tisagenlecleucel infusion
7. Presence of active hepatitis B or hepatitis C (in [Section 16.1 Appendix 1](#)).
8. HIV positive patients.
9. Clinically significant active infection confirmed by clinical evidence, imaging, or positive laboratory tests (e.g., blood cultures, PCR for DNA/RNA, etc.)
10. Any of the following cardiovascular conditions:
 - a. Unstable angina, myocardial infarction, coronary artery bypass graft (CABG), or stroke within 6 months prior to screening,
 - b. LVEF <45% as determined by ECHO or MRA or MUGA at screening.
 - c. NYHA functional class III or IV ([Chavey et al 2001](#)), at screening or within the past 12 months.
 - d. Clinically significant cardiac arrhythmias (e.g., ventricular tachycardia), complete left bundle branch block, high-grade AV block (e.g., bifascicular block, Mobitz type II) and third degree AV block, unless adequately controlled by pacemaker implantation.
 - e. Resting QTcF \geq 450 msec (male) or \geq 460 msec (female) at screening or inability to determine the QTcF interval
 - f. Risk factors for Torsades de Pointes (TdP), including uncorrected hypokalemia or hypomagnesemia, history of cardiac failure, or history of clinically significant/symptomatic bradycardia, or any of the following:
 - i. Long QT syndrome, family history of idiopathic sudden death or congenital long QT syndrome

- ii. Concomitant medication(s) with a “Known Risk of Torsades de Pointes” per crediblemeds.org that cannot be discontinued or replaced by safe alternative medication
- 11. Previous or concurrent malignancy except for curatively treated non-melanoma skin cancers, in situ carcinoma (e.g. cervix, breast, bladder, prostate), and cancers in complete remission for at least 3 years and without evidence of recurrence
- 12. Hypersensitivity to the excipients of tisagenlecleucel or to any other drug product as advised for administration in the study protocol (e.g. lymphodepleting agents, tocilizumab)
- 13. Active neurological autoimmune or inflammatory disorders (e.g., Guillain-Barré Syndrome (GBS), Amyotrophic Lateral Sclerosis (ALS)) and clinically significant active cerebrovascular disorders (e.g., cerebral edema, posterior reversible encephalopathy syndrome (PRES))
- 14. Pregnant or nursing (lactating) women
Note: Women of child-bearing potential must have a negative serum pregnancy test performed within 24 hours before leukapheresis
- 15. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, **unless** they are using highly effective methods of contraception starting from the time of informed consent form (ICF) signature and for:
 - at least 12 months after the tisagenlecleucel infusion and until CART cells are no longer present by qPCR on two consecutive tests for patients in Arm A or patients who crossover.
 - a duration according to local label and physician recommendations for patients randomized to Arm B (SOC). Furthermore, patients may need to also add barrier contraception methods if required by the local label.

Highly effective contraception methods include:

- Total abstinence (when this is in line with the preferred and usual lifestyle of the participant. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
- Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy, or bilateral tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
- Male sterilization (at least 6 months prior to screening). For female participants on the study, the vasectomized male partner should be the sole partner for that participant
- Use of oral, (estrogen and progesterone), injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS), or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception.
- In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking study treatment.

- Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or bilateral tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

Note: If local regulations deviate from the contraception methods listed above to prevent pregnancy, local regulations apply and will be described in the ICF.

In addition, participants must not donate oocytes.

16. Sexually active males who do not use a condom during intercourse starting from the time of ICF signature and for:

- at least 12 months after the tisagenlecleucel infusion and until CAR T-cells are no longer present by qPCR on two consecutive tests for patients in Arm A or patients who crossover.
- a duration according to local label and physician recommendations for patients randomized to Arm B (SOC)

A condom is required for **all** sexually active male participants to prevent them from fathering a child AND to prevent delivery of study treatment via seminal fluid to their partner. In addition, participants must not donate sperm.

17. Patients who, in the investigator's judgment and/or according to clinical standards, have a contradiction to any study procedure or have any other medical condition that may put the patient at unacceptable risk.

No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible participants.

6 Treatment

6.1 Study treatment

6.1.1 Investigational and control drugs

Investigational Drug

Bridging Therapy - For patients randomized to Arm A (tisagenlecleucel) who require optional bridging therapy, the investigator must choose one of the four regimens described under the control arm. Patients that crossover to arm A after failing treatment with SOC chemotherapy may use any type of bridging therapy at the investigator's discretion and are not restricted to the four bridging therapies specified in the protocol in [Section 3](#) and [Section 6.1.1](#) Control Drug.

Radiotherapy that is given for palliative or symptomatic purposes is allowed at any time prior to tisagenlecleucel infusion.

Tisagenlecleucel - Tisagenlecleucel is an autologous cellular immunotherapy product that is comprised of CD3+ T cells that have undergone *ex vivo* T cell activation, gene modification, expansion and formulation in infusible cryomedia.

For details please refer to the [\[Investigational Product Handling Manual and Investigational Product Transport Manual\]](#) and the current version of the [Tisagenlecleucel Investigator's Brochure].

Control Drug (Standard of Care)

For patients randomized to Arm B (SOC therapy), investigators are to choose one of the following regimens. Immunochemotherapy should start as soon as possible after randomization, and no later than 7 days after randomization.

Rituximab (375 mg/m² starting on the first day prior to chemotherapy on each cycle),

- R-ICE: etoposide (100 mg/m² per day) on days 1 through 3, ifosfamide (5,000 mg/m²) infused continuously for 24 hours on day 2 with mesna, carboplatin (area under the curve (AUC) = 5; maximum dose, 800 mg) on day 2 ([Kewalramani et al 2004](#)). Cycles repeated every 21 days.
- R-DHAP: cisplatin (100 mg/m²) on day 1 via continuous 24-hour infusion, followed on day 2 by cytarabine (2 g/m²) in a 3-hour infusion repeated after 12 hours, dexamethasone (40 mg/d) for 4 consecutive days ([Velasquez et al 1998](#)). Cycles repeated every 21 days.
- R-GDP: gemcitabine 1000 mg/m² on days 1 and 8, cisplatin 75 mg/m² on day 1, dexamethasone (40 mg/d) for 4 consecutive on days 1 through 4 ([Baetz et al 2003](#)). Cycles repeated every 21 days.
- R-GemOx - gemcitabine and oxaliplatin at the doses of 1000 mg/m² and 100 mg/m², respectively, on day 2. ([Mounier et al 2013](#)). Cycles repeated every 15 days.

For patients randomized to Arm B (SOC therapy), a change in immunochemotherapy is required if the patient achieves a response which is not sufficient to allow HSCT, and change in treatment is in the best interest of the patient. Investigators should choose one of the four regimens above in an effort to achieve a response that allows the patient to proceed to transplant. Patients who are deemed no longer eligible for HSCT (e.g. adverse event, poor tolerance to immunochemotherapy, worsening of performance status) after two cycles of immunochemotherapy may proceed to treatment with ibrutinib or lenalidomide.

Radiotherapy that is given for palliative or symptomatic purposes is allowed at any time prior to HSCT.

For patients proceeding to autologous HSCT, mobilization of stem cells will be performed during cycle 2 and/or cycle 3 of salvage therapy according to local policy using granulocyte-colony stimulating factor (G-CSF). In the case of a mobilization failure, additional attempts at mobilization or operative bone marrow harvest can be performed according to local policy. Leukapheresis and cryopreservation will be performed according to local procedures.

Participants with CR or PR after the 2 cycles (SOC 1) of salvage therapy and adequate stem cell collection may receive an optional 3rd cycle of salvage therapy before transplant, or may proceed directly to transplant after 2 cycles. At the investigator's discretion, patients in PR may change to one of the other 4 regimens. Every effort should be attempted to have SOC patients

proceed to transplant, if deemed in the best interest of the patient. Patients should receive high dose chemotherapy approximately 4-6 weeks after the last cycle of salvage therapy.

In countries where the drugs are available, and can be used for this indication, the BEAM regimen is to be used. BEAM is recommended to be dosed as follows (days shown are relevant to HSCT):

- Carmustine 300 mg/m² i.v., Day -6,
- Etoposide 200 mg/m² i.v., Day -5, -4, -3, -2
- Cytarabine 200 mg/m² every 12 hours (q12hr, 2 doses) i.v., Day -5, -4, -3, -2,
- Melphalan 140 mg/m² i.v., Day -1

If BEAM is not used, the HDCT regimen will be in accordance with local policy. Before any participants are randomized, the HDCT regimen must be documented in the institutional treatment policy. The procedure for HSCT will be in accordance with local policy. Prophylaxis of CNS disease using intrathecal dosing of cytotoxic regimens is permitted and will be according to local policy.

The date of HSCT will be recorded in IRT.

6.1.2 Tisagenlecleucel pre-infusion evaluation

If any of the following criteria is met, tisagenlecleucel infusion must be delayed until resolution. If the period of delay is more than 4 weeks from completing lymphodepletion and there is no significant cytopenia (see [Section 6.1.4.2](#)) lymphodepletion should be repeated, and these criteria will need to be re-checked prior to tisagenlecleucel infusion. In case of any doubt on fulfillment of pre-infusion evaluation criteria, the medical monitor may be contacted.

The investigator will be required to sign the tisagenlecleucel pre-infusion checklist stating fulfillment of pre-infusion criteria within 24 hours prior to tisagenlecleucel infusion. Criteria must continue to be monitored after the form is signed until the time of infusion in case of any worsening of status which would preclude tisagenlecleucel infusion.

The tisagenlecleucel pre-infusion criteria/checklist is found below:

1. Rapidly progressing primary disease: Not limited to radiological evidence, but also including signs and symptoms of disease progression (i.e. significant rising LDH values) Particular attention must be placed on any significant rising of LDH value and on declining ECOG PS: e.g. patients with an ECOG PS of 3 **must not** be infused, while patients with ECOG PS of 2 must have their full clinical picture considered before proceeding to infusion
2. Clinical evidence of CNS involvement by primary disease
3. Laboratory abnormalities that, in the opinion of the investigator, may impact participant safety or the participants' ability to receive tisagenlecleucel.
4. Following clinical abnormalities:
 - Pulmonary: Requirement for supplemental oxygen to keep saturation greater than 90% or presence of progressive radiographic abnormalities on chest x-ray
 - Cardiac arrhythmia not controlled with medical management

- Hypotension requiring vasopressor support
- Clinically significant active infection confirmed by clinical evidence, imaging, or positive laboratory tests (e.g., blood cultures, PCR for DNA/RNA, , etc.)

Note: HBV, HCV, and HIV must be repeated, if the interval between testing prior to lymphodepletion and tisagenlecleucel infusion exceeds 8 weeks.

5. A significant change in clinical status that would, in the opinion of the investigator, increase the risk of adverse events associated with tisagenlecleucel.
6. Toxicities from chemotherapy (including lymphodepletion)
7. Prohibited concomitant medications as described in [Section 6.2.2](#).
8. Positive influenza test within 10 days prior to tisagenlecleucel infusion (please refer to [Table 8-2](#)). **Note:** If the participant is positive for influenza, oseltamivir phosphate or zanamivir should administered for 10 days as preventative treatment (see Tamiflu® or Relenza® package insert for dosing). The participant must complete their 10 day preventative treatment course **prior** to receiving tisagenlecleucel. The test does not need to be repeated prior to tisagenlecleucel infusion however if flu-like or respiratory signs and symptoms are present, tisagenlecleucel infusion should be delayed until the participant is asymptomatic. For participants residing in the northern hemisphere (e.g. United States, Canada, Europe and Japan), influenza testing is required during the months of October through May (inclusive). For participants residing in the southern hemisphere such as Australia, influenza testing is required during the months of April through November (inclusive). For participants with significant international travel, both calendar intervals above may need to be considered.
9. Women of child-bearing potential must have a negative serum pregnancy test performed within 24 hours prior to tisagenlecleucel infusion.

6.1.3 Additional safety procedures prior to tisagenlecleucel infusion

Tumor lysis syndrome (TLS)

The risk of tumor lysis syndrome (TLS) is dependent on disease burden. Participants will be closely monitored both before and after lymphodepleting chemotherapy and the tisagenlecleucel infusion, including blood tests for potassium and uric acid. Participants with elevated uric acid or high tumor burden will receive prophylactic allopurinol, or a non-allopurinol alternative (e.g. febuxostat).

Infections

Infection prophylaxis with regard to lymphodepletion and other additional treatments should follow local guideline. Prior to tisagenlecleucel infusion, infection prophylaxis should follow standard guidelines based on the degree of preceding immunosuppression. In patients with low immunoglobulin levels pre-emptive measures such as infection precautions, antibiotic and antifungal prophylaxis and immunoglobulin replacement should be taken according to age and standard guidelines.

Cytokine Release Syndrome

Prior to tisagenlecleucel infusion 2 doses of tocilizumab per participant (for the first 3 weeks after tisagenlecleucel infusion) must be confirmed as available by the local pharmacy and must be available for infusion within 2 hours of physician order for the management of CRS related adverse events (see [Section 6.6.2.1](#) for details).

Premedication

Adverse effects from T cell infusions can include fever, chills and/or nausea. All participants should be pre-medicated with acetaminophen (paracetamol) and diphenhydramine or another H1 antihistamine approximately 30 to 60 minutes prior to infusion. These medications can be repeated every 6 hours as needed. Non-steroidal anti-inflammatory medication may be prescribed if the participant continues to have fever not relieved with acetaminophen (paracetamol). Steroids should NOT be used for premedication. It is recommended that participants NOT receive systemic corticosteroids other than physiologic replacement, except for serious emergency, since this may have an adverse effect on tisagenlecleucel cell expansion and function. For more information on managing toxicities related to tisagenlecleucel treatment, please refer to [Section 6.6.2](#).

Supportive care

Local guidelines will be followed for the supportive care of immunosuppressed and chemotherapy treated participants. All blood products administered should be irradiated. For details about prohibited concomitant medications and non-drug therapies please refer to [Section 6.2.2](#).

6.1.4 Additional study treatments

6.1.4.1 Optional bridging therapy

For patients randomized to Arm A (tisagenlecleucel), there will be an estimated delay of treatment while tisagenlecleucel is manufactured and before it is available on-site. During this time, the treating physician will have the option to treat the patient according to local guidance, product label, and the medical condition of the patient. If bridging therapy is prescribed, the investigator should use one of the four prescribed regimens in [Section 6.1.1](#). During this optional bridging therapy period, all safety evaluations should follow the visit evaluation schedule and local standard of care guidelines and be captured in source documentation or database where denoted by [Table 8-2](#).

Patients that crossover to arm A after failing treatment with SOC chemotherapy may use any type of bridging therapy at the investigator's discretion and are not restricted to the four bridging therapies specified in the protocol in [Section 3](#) and [Section 6.1.1](#).

If optional bridging therapy is interrupted or delayed, the reason must be documented in source files and captured in the appropriate eCRF.

The start of bridging chemotherapy visit start should be registered in IRT.



6.1.4.2 Lymphodepleting chemotherapy

Prior to tisagenlecleucel infusion, each patient should undergo lymphodepletion, unless the patient has a significant cytopenia (e.g. WBC <1,000 cells/ μ L, absolute lymphocyte count <200/ μ L) or any condition that, in the investigator's opinion, precludes lymphodepletion.

If lymphodepleting chemotherapy is NOT required, a visit should still occur during this time window, and required assessments according to [Table 8-2](#) should be completed.

The lymphodepleting chemotherapy start date should be registered in IRT.

Lymphodepletion should start within one week before tisagenlecleucel infusion, which means that tisagenlecleucel will be infused 2 to 6 days after lymphodepletion is completed depending on the lymphodepleting regimen. The availability of tisagenlecleucel must be confirmed prior to starting the lymphodepleting chemotherapy. Lymphodepletion may be repeated in case tisagenlecleucel has been delayed by more than 4 weeks (see [Section 6.1.4.1](#)). The preferred regimen is as follows:

- Fludarabine (25 mg/m² intravenously [i.v.] daily for 3 doses)
- Cyclophosphamide (250 mg/m² i.v. daily for 3 doses starting with the first dose of fludarabine)

Note: Adverse effects of fludarabine can include severe nervous system events of seizure, agitation, blindness, coma and death. Instances of life-threatening and sometimes fatal autoimmune phenomena such as hemolytic anemia, autoimmune thrombocytopenia/thrombocytopenic purpura (ITP), Evans syndrome, and acquired hemophilia have been reported to occur after one or more cycles of treatment with fludarabine phosphate injection. It may also severely decrease bone marrow function ([Fludarabine full prescribing information](#)).

Cyclophosphamide toxicities include cardiac dysfunction. Acute cardiac toxicity has been reported with doses as low as 2.4 g/m² to as high as 26 g/m², usually as a portion of an intensive antineoplastic multi-drug regimen or in conjunction with transplantation procedures. In a few instances with high doses of Cyclophosphamide, severe, and sometimes fatal, congestive heart failure has occurred after the first Cyclophosphamide dose. Severe marrow suppression is seen and occasional anaphylactic reactions have been reported. Hemorrhagic cystitis, pulmonary toxicity (pneumonitis, pulmonary fibrosis and pulmonary veno-occlusive disease leading to respiratory failure) and veno-occlusive liver disease may occur ([Cyclophosphamide full prescribing information](#)).

If there was previous grade IV hemorrhagic cystitis with cyclophosphamide, or the patient demonstrated resistance to a previous cyclophosphamide-containing regimen, then the following regimen should be used:

- Bendamustine 90 mg/m² i.v. daily for 2 days

Note: Adverse effects of bendamustine include severely decreased bone marrow function, nausea, vomiting and diarrhea; jaundice may occur, including without other signs of hepatic dysfunction. Fatal and serious cases of liver injury have been reported ([Bendamustine full prescribing information](#)).

No other regimen is allowed for lymphodepletion.

Female patients of childbearing potential must have a negative serum pregnancy test within 24 hours prior to the start of lymphodepleting therapy. If the patient does not require lymphodepleting therapy, she should still have a negative pregnancy test at the required visit that takes place within one week from tisagenlecleucel infusion.

6.1.5 Treatment arms

Participants will be assigned at the randomization visit to one of the following 2 treatment arms/groups in a ratio of 1:1.

- **Arm A:** A single dose of 0.6 to 6.0×10^8 of CAR positive viable autologous tisagenlecleucel transduced T cells administered via intravenous infusion. The patient may also have up to 3 days of lymphodepleting chemo prior to tisagenlecleucel infusion as described in [Section 6.1.4.1](#). Optional platinum based bridging immunochemotherapy can be given during the time period while tisagenlecleucel is being manufactured (after randomization and prior to lymphodepleting chemotherapy) as per investigator assessment as described in [Section 6.1.4.2](#).
- **Arm B:** SOC immunochemotherapy including, in suitable patients, autologous HSCT, as per local guidelines. Ibrutinib and lenalidomide are also allowed for patients who are deemed no longer eligible for HSCT (e.g. adverse event, poor tolerance to immunochemotherapy, worsening of performance status) after two cycles of immunochemotherapy . .

6.1.6 Treatment duration

For patients randomized to Arm A, a single dose of tisagenlecleucel will be administered. Prior to tisagenlecleucel infusion, patients may receive optional bridging chemotherapy while tisagenlecleucel is manufactured, and then may receive lymphodepleting chemotherapy as outlined in [Section 6.1.4.1](#).

Patients randomized to Arm B will continue to receive immunochemotherapy as per local guidelines or until patients undergo autologous HSCT.

Patients will continue treatment in Arm B until they experience any of the following:

- Disease progression or continuous SD at or after the week 12 (± 1 week) assessment (confirmed by the BIRC).
Note: All patients who have disease progression or continuous SD at or after the week 12 (± 1 week) assessment determined by the local investigator will require an expedited tumor response review (within 5 business days) by the BIRC. SOC chemotherapy will continue until progressive disease or continuous SD at or after the week 12 (± 1 w) assessment has been confirmed by the BIRC if clinically acceptable. In cases of discordance (i.e., BIRC does not confirm the site's assessment) for as long as it is clinically acceptable the patient should not be discontinued from study treatment.
- Start of a new experimental (i.e., patient is enrolled in a clinical trial) anti-cancer therapy after the week 12 (± 1 week) assessment
- Pregnancy
- Treatment is discontinued at the discretion of the investigator or patient

- Lost to follow-up
- Death
- Study terminated by Sponsor

Patients, that have discontinued early for reasons other than BIRC confirmed PD or continuous SD at or after the week 12 (\pm 1 week) assessment, loss to follow-up, death, or study termination, will continue efficacy assessments as per protocol until BIRC confirmation of EFS event.

6.1.7 Dosing regimen

Tisagenlecleucel Treatment Strategy

For patient randomized to the tisagenlecleucel, the recommended dose will consist of a single intravenous (i.v.) infusion of $0.6 - 6.0 \times 10^8$ CAR-positive viable T cells.

For the optional bridging chemotherapy administration please follow the approved label, required country, and institution guidelines for one of the four prescribed regimens in [Section 6.1.1](#). Patients that crossover to arm A after failing treatment with SOC chemotherapy may use any type of bridging therapy at the investigator's discretion and are not restricted to the four bridging therapies specified in the protocol in Section 3 and Section 6.1.1 and should follow the approved label, required country, and institution guidelines.

In rare cases tisagenlecleucel may present with out-of-specification results of the release testing. Where the administration of the product is necessary to avoid an immediate significant hazard to the patient and taking into account the alternative options for the patient and the consequences of not receiving tisagenlecleucel, the supply of the product may be justified upon request from the treating physician. Tisagenlecleucel will then be provided based on the evaluation of the risks and the confirmation of the treating physician to accept the product.

Tisagenlecleucel infusion will begin 2 to 6 days after completion of lymphodepleting chemotherapy.

The day of (but prior to) the tisagenlecleucel infusion, patients will undergo assessments described in [Table 8-2](#). Final tisagenlecleucel infusion pre-requisites (including an ECG and a rapid influenza test) will be checked prior to infusion as per [Section 6.1.2](#).

Tisagenlecleucel transduced T cells will be given as a single dose within 0.6 to 6.0×10^8 tisagenlecleucel transduced cells. Vital signs will be monitored before, during, and following tisagenlecleucel infusion (per [Table 8-2](#)). An additional blood sample will be collected post-infusion for tisagenlecleucel cellular kinetics assessment as per [Table 8-12](#) and [Table 8-13](#).

The tisagenlecleucel infusion visit should be registered in IRT. If the patient is not infused with tisagenlecleucel, the reason for not infusing should be recorded in IRT.

Standard of Care Treatment Strategy

For the SOC immunochemotherapy and HDCT administration, please follow the approved label, required country, and institution guidelines for one of the four prescribed regimens in [Section 6.1.1](#). Stem cell collection, HSCT, and eligibility for transplant should be done as per institutional guidelines.



Modifications to the dose based on individual patient tolerability and institution's policy are allowed. Modifications/substitutions to the drug combinations of each regimen as per local clinical practice may be made only after discussion with the Novartis global medical representative (e.g., substituting R-DHAOX for R-DHAP). If SOC therapy is interrupted or delayed, the reason must be documented in source files and captured in the appropriate eCRF.

The start of SOC visit should be registered in IRT.

6.2 Other treatment(s)

6.2.1 Concomitant therapy

Clinically significant prescription and nonprescription medication, excluding vitamins, and herbal and nutritional supplements, and procedure-related (inpatient or outpatient) medications taken by the participant during the 30 days prior to screening will be recorded, as required by the modified reporting criteria in [Section 16.3 Appendix 3](#).

At every visit following the screening visit up to the end of the study, concomitant medications will be recorded in the medical record and on the appropriate CRF. During selected trial phases, concomitant medication collection will be modified as outlined in [Section 16.3 Appendix 3](#). Modified collection of concomitant medication information during these periods is designed to capture tisagenlecleucel -related toxicity, severity, interventions and response/resolution following intervention. Any additions, deletions, or changes of these medications will be documented. A safety follow-up visit should occur 8 weeks after last treatment administration or prior to starting new anticancer therapy, whichever occurs first. After this safety follow-up visit occurs, for patients who receive tisagenlecleucel concomitant medication collection will be modified as outlined in [Section 16.3 Appendix 3](#) and CRF Completion Guidelines (CCGs). Patients who do not receive tisagenlecleucel do not require reporting of concomitant medications after the safety follow-up visit. Modified collection of concomitant medication information during these periods is designed to capture tisagenlecleucel -related toxicity, severity, interventions and response/resolution following intervention. Any additions, deletions, or changes of these medications will be documented.

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication. If in doubt the investigator should contact the Novartis medical monitor before randomizing a participant or allowing a new medication to be started. If the participant is already enrolled, contact Novartis to determine if the participant should continue participation in the study. Drugs that cause QTc prolongation and/or "Torsades de Pointes" per crediblemeds.org should be used only if clinically indicated as per Investigator's discretion.

6.2.2 Prohibited concomitant medication and non-drug therapy

The participant must be asked to notify the investigational site about any new medications he/she takes after the start of the study drug. All medications (other than study drug) and significant non-drug therapies (including physical therapy, herbal/natural medications and blood transfusions) administered during the study must be listed on the appropriate CRFs. For

medication restrictions before leukapheresis, please refer to the recent [\[Investigational Leukapheresis, Cryopreservation and Scheduling Manual\]](#).

Medication restrictions related to tisagenlecleucel infusion are specified below:

1. **Steroids:** Therapeutic doses of steroids must be stopped >72 hours or 5 half-lives, whichever is greater, prior to tisagenlecleucel infusion. However, the following physiological replacement doses of steroids are allowed: ≤ 40 mg/day hydrocortisone or equivalent
2. **Steroids or other immunosuppressant drugs** should NOT be used as pre-medication for tisagenlecleucel therapy (refer to [Section 6.1.3](#)) or following tisagenlecleucel infusion, except as required for physiological glucocorticoid replacement therapy, or under life threatening circumstances. Use of steroids with blood product administration should be eliminated just prior to and following tisagenlecleucel if possible or at least minimized.
3. **Antibody use** except anti-CD20 therapy (e.g., rituximab) should not be used within 4 weeks prior to tisagenlecleucel infusion.
4. **CNS disease intrathecal prophylaxis** must be stopped > 1 week prior to tisagenlecleucel infusion (e.g. intrathecal methotrexate)
5. **Radiation therapy** must be stopped >2 weeks prior to tisagenlecleucel infusion
6. **Investigational therapies** must not be used at any time while on study until the first progression following tisagenlecleucel infusion
7. **Live vaccines** must not be used in tisagenlecleucel recipients for at least 6 weeks prior to lymphodepletion and during tisagenlecleucel treatment until immune recovery
8. Since **myeloid growth factors**, particularly granulocyte macrophage colony stimulating factor (GM-CSF), have the potential to worsen CRS (if it occurs), these are not recommended during the first 3 weeks after tisagenlecleucel infusion or until CRS has resolved.
9. **Anti-proliferative therapies**, other than lymphodepletion, including low dose daily or weekly maintenance chemotherapy should not be used within 2 weeks prior to infusion.
10. **Short acting drugs** used to treat primary disease (e.g. hydroxyurea, tyrosine kinase inhibitors, lenalidomide, ibrutinib) must be stopped > 72 hours prior to tisagenlecleucel

6.3 Participant numbering, treatment assignment, randomization

6.3.1 Participant numbering

Each participant is identified in the study by a Participant Number (Participant No.), that is assigned when the participant is first enrolled for screening and is retained as the primary identifier for the participant throughout his/her entire participation in the trial. The Participant No. consists of the Center Number (Center No.) (as assigned by Novartis to the investigative site) with a sequential participant number suffixed to it, so that each participant is numbered uniquely across the entire database. Upon signing the informed consent form, the participant is assigned to the next sequential Participant No. available.

The investigator or designated staff will contact the IRT and provide the requested identifying information for the participant to register them into the IRT. Once assigned, the Participant No.

must not be reused for any other participant. If the participant fails to start treatment for any reason, the reason will be entered into the appropriate CRF page.

6.3.2 Treatment assignment, randomization

The following methods have been used to minimize bias in treatment assignment. The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from participants and investigator staff. A participant randomization list will be produced by the IRT provider, or by a delegate under Novartis supervision, using a validated system that automates the random assignment of participant numbers to randomization numbers. These randomization numbers are linked to the different treatment arms.

Randomization will be stratified by remission duration (refractory or relapse <6 months from last dose of first line immunochemotherapy vs. relapsed 6 to 12 months from last dose of first line immunochemotherapy), IPI (<2 vs. ≥ 2) at study entry, and region (North America vs. Rest of World). IPI will be assessed as follows as shown in [Table 6-1](#).

For the purposes of stratification, refractory is defined as subjects who did not achieve CR on first line immunochemotherapy to current lymphoma. Refractory patients include any patient with biopsy-proven PR after 6 cycles of first line immunochemotherapy.

For the purposes of stratification, relapsed is defined as subjects who had CR on first line therapy to current lymphoma and relapsed prior to the study.

Table 6-1 Defined risk factors and risk groups of International Prognostic Index (IPI)

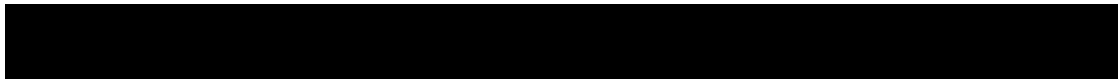
Risk Factors	
<ul style="list-style-type: none">• Age > 60 years (at time of ICF)• Performance Status 2 – 4 (at screening)• Tumor Stage III or IV (at study entry based on re-staging using screening PET/CT)• LDH > 1xULN (as per central lab report)• Extranodal site involvement (including bone marrow, GI tract, liver, lung, skin), >1 (at study entry based on re-staging using screening PET/CT)	
Number of Risk Factors	Risk Group
0-1	1 – low
2	2 – low intermediate
3	3 – high intermediate
4-5	4 – high

The randomization scheme for participants will be reviewed and approved by a member of the Randomization Office.

Participants in the China extension cohort will be stratified by remission duration and IPI. The region stratum is not applicable to this specific cohort.

6.4 Treatment blinding

Treatment will be open to participants, investigator staff, persons performing the assessments, and the CTT.



6.5 Dose modification

Tisagenlecleucel is administered as a single dose and therefore dose modification is not applicable as participants will receive a single intravenous (i.v.) infusion of $0.6 - 6.0 \times 10^8$ CAR-positive viable T cells.

For patients randomized to SOC therapy or patients receiving optional bridging chemotherapy, modifications to the dose based on individual patient tolerability and institution's policy are allowed. Modifications/substitutions to the drug combinations of each regimen as per local clinical practice may be made only after discussion with the Novartis global medical representative (eg. substituting R-DHAOX for R-DHAP)).

In exceptional circumstances when the investigator feels that patient safety would be compromised unless an anticancer treatment outside of the recommended regimens is administered, the Novartis medical monitor should be contacted prior to initiation.

6.5.1 Follow-up for toxicities

For patients randomized to SOC the investigator should monitor any organ toxicities of SOC and take according measures as per local labeling and apply local standard of medical practice.

6.5.1.1 Follow up on potential drug-induced liver injury (DILI) cases

Patients with transaminase increase combined with total bilirubin (TBIL) increase may be indicative of potential drug induced liver injury (DILI), and should be considered as clinically important events.

The threshold for potential DILI may depend on the participant's baseline AST/ALT and TBIL value; participants meeting any of the following criteria will require further follow-up as outlined below:

- For participants with normal ALT and AST and TBIL value at baseline: AST or ALT $> 3.0 \times \text{ULN}$ combined with TBIL $> 2.0 \times \text{ULN}$
- For participants with elevated AST or ALT or TBIL value at baseline: [AST or ALT $> 2 \times \text{baseline AND } > 3.0 \times \text{ULN}$] OR [AST or ALT $> 8.0 \times \text{ULN}$], combined with [TBIL $> 2 \times \text{baseline AND } > 2.0 \times \text{ULN}$]

Medical review needs to ensure that liver test elevations are not caused by cholestasis, defined as alkaline phosphatase (ALP) elevation $> 2.0 \times \text{ULN}$ with R value < 2 in participants without bone metastasis, or elevation of ALP liver fraction in participants with bone metastasis.

Note: (The R value is calculated by dividing the ALT by the ALP, using multiples of the ULN for both values. It denotes whether the relative pattern of ALT and/or ALP elevation is due to cholestatic ($R \leq 2$), hepatocellular ($R \geq 5$), or mixed ($R > 2$ and < 5) liver injury).

In the absence of cholestasis, these participants should be immediately discontinued from study treatment, and repeat liver function test (LFT) as soon as possible, preferably within 48 hours from the awareness of the abnormal results. The evaluation should include laboratory tests, detailed history, physical assessment and the possibility of liver metastasis or new liver lesions, obstructions/compressions, etc.

1. Laboratory tests should include ALT, AST, albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, GGT, prothrombin time (PT)/international normalized ratio (INR) and alkaline phosphatase.
2. A detailed history, including relevant information, such as review of ethanol, concomitant medications, herbal remedies, supplement consumption, history of any pre-existing liver conditions or risk factors, should be collected.
3. Further testing for acute hepatitis A, B, C or E infection and liver imaging (e.g. biliary tract) may be warranted.
4. Obtain cellular kinetics sample, as close as possible to last dose of study treatment
5. Additional testing for other hepatotropic viral infection (cytomegalovirus (CMV), EBV or herpes simplex virus (HSV), autoimmune hepatitis or liver biopsy may be considered as clinically indicated or after consultation with specialist/hepatologist.

All cases confirmed on repeat testing meeting the laboratory criteria defined above, with no other alternative cause for LFT abnormalities identified should be considered as “medically significant”, thus, met the definition of serious adverse event (SAE) and reported as SAE using the term “potential drug-induced liver injury”. All events should be followed up with the outcome clearly documented

6.6 Additional treatment guidance


6.6.1 Treatment compliance

Novartis has established methods to ensure full traceability between the patient’s autologous leukapheresis and the tisagenlecleucel product in line with the requirements outlined in Regulation (EC) 1394/2007, the Directive 2004/23/EC as well as the rules and principles of the European Union (EU) “Detailed guidelines on good clinical practice (GCP) specific to advanced therapy medicinal Products” and 21 CFR 1271.250 and 21 CFR 1271.290. The data contributing to the full traceability of the cells are stored for a minimum of 30 years. Any product quality complaints are documented by the clinical site and reported to the Novartis Clinical Supplies Quality Assurance (QA) Department. A unique patient identifier will be used in order to maintain the chain of identity between the autologous leukapheresis product and the tisagenlecleucel batch and the link between patient identity and unique patient identifier will be confirmed prior to infusion. The investigational product handling manual provides an overview of how the company ensures that the cells which are procured, processed, stored, and distributed by or on behalf of Novartis can be traced from leukapheresis to infusion.

The investigator or designee must maintain an accurate record of the drug receipt logs and Drug Accountability Forms. Drug accountability will be reviewed by the field monitor during site visits and prior to the completion of the study. At study close-out, and, as appropriate during the course of the study, the investigator will return a copy of the completed drug accountability forms to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

6.6.1.1 Tisagenlecleucel compliance

As a single administration study, compliance will be assessed by the investigator and/or study personnel and captured in the Drug Accountability Form.



6.6.1.2 SOC, Optional Bridging Chemotherapy, and Lymphodepleting Chemotherapy compliance

For patients receiving SOC therapy either on Arm A as optional bridging to tisagenlecleucel treatment or Arm B as comparator arm treatment, compliance will be assessed by the investigator and/or study personnel and captured in the Drug Accountability Form, where applicable. Any dose interruptions or dose modifications should be documented on the appropriate eCRF.

For patients receiving lymphodepleting chemotherapy, compliance will be assessed by the investigator and/or study personnel and captured in the Drug Accountability Form, where applicable. Any dose interruptions or dose modifications should be documented on the appropriate eCRF

6.6.2 Recommended treatment for adverse events

Participants infused with tisagenlecleucel are at risk of developing a number of severe and serious AEs that are related either to tisagenlecleucel itself, other therapies (e.g. immunochemotherapy) and conditions concurrent with the participant's primary disease. Following tisagenlecleucel infusion, participants can be discharged from the treating site only if, in the investigator's opinion, they do not demonstrate any adverse events or worsening of underlying diseases. This chapter describes the management of such AEs.

Drug and non-drug therapies used to treat AEs must be recorded on appropriate CRFs.

6.6.2.1 Cytokine Release Syndrome (CRS)

Ensure that 2 doses of tocilizumab per patient are available on site prior to infusion of tisagenlecleucel. Hospitals should have timely access to additional doses of tocilizumab. Supportive care, tocilizumab, and corticosteroids have been used for effective management of CRS. Prompt responses to tocilizumab have been seen in most participants. See full local prescribing information to use tocilizumab.

Identify CRS based on clinical presentation (see [Section 4.5.1.1](#)). Evaluate for and treat other causes of fever, hypoxia, and hypotension. Although signs and symptoms of CRS occur in most cases within 1-14 days after tisagenlecleucel infusion, monitor patients for signs or symptoms of CRS for at least 4 weeks after treatment with tisagenlecleucel. Counsel patients to seek immediate medical attention should signs or symptoms of CRS occur at any time. Participants will be required to remain proximal to the treating site for the first 4 weeks.

At the first sign of CRS, immediately evaluate patient for hospitalization and institute treatment with supportive care, tocilizumab and/or corticosteroids as indicated.

A detailed treatment algorithm for the management of CRS and definition of high dose vasopressors ([Lee et al 2014](#)) is presented below in [Table 6-2](#) and [Table 6-3](#) respectively. The CRS management algorithm is a guideline and the investigator may use discretion or modify the treatment approach as needed for an individual participant.

Table 6-2 CRS management

CRS severity	Symptomatic treatment	Tocilizumab	Corticosteroids
Mild symptoms requiring symptomatic treatment only e.g. low fever, fatigue, anorexia, etc.	Exclude other causes (e.g. infection) and treat specific symptoms with e.g. antipyretics, anti-emetics, anti-analgesics, etc. If neutropenic, administer antibiotics per local guidelines	Not applicable	Not applicable
Symptoms requiring moderate intervention: - high fever - hypoxia - mild hypotension	Antipyretics, oxygen, intravenous fluids and/or low dose vasopressors as needed.		
Symptoms requiring aggressive intervention: Hypoxia requiring high-flow oxygen supplementation or Hypotension requiring high-dose or multiple vasopressors	High-flow oxygen Intravenous fluids and high-dose* vasopressor/s Treat other organ toxicities as per local guidelines	If no improvement after symptomatic treatment administer tocilizumab i.v. over 1 hour: - 8 mg/kg (max. 800 mg) if body weight ≥ 30 kg - 12 mg/kg if body weight <30 kg	If no improvement within 12-18 hours of tocilizumab, administer a daily dose of 2 mg/kg i.v. methylprednisolone (or equivalent) until vasopressor and oxygen no longer need, then taper**
Life-threatening symptoms: - Hemodynamic instability despite i.v. fluids and vasopressors - Worsening respiratory distress - Rapid clinical deterioration	Mechanical ventilation Intravenous fluids and high-dose* vasopressor/s Treat other organ toxicities as per local guidelines	If no improvement, repeat every 8 hours (max total of 4 doses)**	

*Refer to [Table 6-3](#) for definition of high dose vasopressors

** If no improvement after tocilizumab and steroids, consider other anti-cytokine and anti-T cell therapies. These therapies may include siltuximab (11 mg/kg i.v. over 1 hour), high doses of steroids (e.g. high dose methylprednisolone or equivalent steroid dose according to local ICU practice) cyclophosphamide, anti-thymocyte globulin (ATG) or alemtuzumab.

Table 6-3 Definition of high dose vasopressor use

Vasopressor	Dose to be given for ≥ 3 hours
Norepinephrine monotherapy	≥ 20 mcg/min
Dopamine monotherapy	≥ 10 mcg/kg/min
Phenylephrine monotherapy	≥ 200 mcg/min
Epinephrine monotherapy	≥ 10 mcg/min
If on vasopressin	Vasopressin + norepinephrine equivalent (NE) of ≥ 10 mcg/min*
If on combination vasopressors (not vasopressin)	NE of ≥ 20 mcg/min*
Vasopressin and Septic Shock Trial (VASST) Norepinephrine Equivalent Equation: NE dose = [norepinephrine (mcg/min)] + [dopamine (mcg/kg/min) ÷ 2] + [epinephrine (mcg/min)] + [phenylephrine (mcg/min) ÷ 10] (Lee et al 2014)	

Any therapies given for CRS need to be captured in the appropriate CRF.

The management of CRS is based solely upon clinical parameters as described in [Section 4.5.1.1](#). Ferritin, C-reactive protein (CRP) and serum cytokine levels should NOT be used for clinical management decisions. Cases of transient left ventricular dysfunction, as assessed by ECHO, have been reported in some patients with severe (Grade 4) CRS. Therefore consideration should be given to monitoring cardiac function by ECHO during severe CRS, especially in cases with prolonged severe hemodynamic instability, delayed response to high dose vasopressors, and/or severe fluid overload.

6.6.2.2 Neurologic adverse events

Neurologic events, primarily reflective of encephalopathy and delirium, may occur after tisagenlecleucel infusion. These present clinically as signs and symptoms of varying severity including: confusion, disorientation, agitation, aphasia, somnolence and tremors. In severe cases seizures, motor weakness, incontinence, impaired consciousness, increased intracranial pressure, and cerebral edema may be concurrent to, following the resolution or in the absence of CRS. Patients should be monitored for neurologic events, diagnostically worked-up and managed depending on the underlying pathophysiology and in accordance to local standard of care.

Evaluation:

Thorough neurological examination, with frequent monitoring and determination of CTCAE v5.0 grading, as well as ASTCT ICANS Consensus Grading ([Table 4-4](#))

- Diagnostic work up to evaluate potential secondary causes:
 - Brain imaging (CT scan and/or MRI): to exclude intracranial hemorrhage, disease relapse, evidence suggestive of infection or cerebral edema.
 - Lumbar puncture for CSF evaluation, if applicable.
 - Chemistry laboratory testing
 - Electroencephalography (EEG)

Management:

- If the neurological event is concurrent with CRS please refer to [Table 6-2](#). CRS algorithm table for treatment recommendation.
- Consider anti-seizure medications (e.g. Levetiracetam) for patient at high risk (prior history of seizure) or administer in the presence of seizure
- For encephalopathy, delirium or associated events: appropriate treatment and supportive care should be implemented as per local standard of care. In worsening events, consider a short course of steroids ([Neelapu et al 2018](#), [Teachey et al 2018](#))

6.6.2.3 Hypersensitivity including acute infusion reactions

Patients should be monitored for signs and symptoms of hypersensitivity following initiation of tisagenlecleucel infusion and treated appropriately. Tisagenlecleucel is contraindicated in patients with known hypersensitivity to tisagenlecleucel or to any component of the product formulation.

As appropriate, prophylactic medications should be administered to minimize the risk of immediate hypersensitivity including acute infusion reactions. It is recommended to pre-medicate all patients with acetaminophen (paracetamol) and diphenhydramine or another H1 antihistamine within approximately 30-60 minutes prior to tisagenlecleucel infusion. These medications can be repeated every 6 hours as needed. Non-steroidal anti-inflammatory medication may be prescribed for fever not responding to acetaminophen. Steroids should not be used for premedication. Systemic corticosteroids should only be used for severe conditions.

Should emergency treatment be required in the event of life-threatening hypersensitivity or other infusion-related reaction, supportive therapy such as oxygen and drug treatment should be given according to local institutional guidelines. Patients should be evaluated and carefully monitored until complete resolution of signs and symptoms.

6.6.2.4 Tumor lysis syndrome (TLS)

Patients should be closely monitored for signs and symptoms of TLS both before and after lymphodepleting chemotherapy and tisagenlecleucel infusion including relevant laboratory tests. To minimize risk of TLS, patients with elevated uric acid or high tumor burden should receive allopurinol, or an alternative prophylaxis, prior to tisagenlecleucel infusion. Events should be managed according to local guidelines.

6.6.2.5 Infections

Patients with active, uncontrolled infection should not start tisagenlecleucel treatment until the infection is resolved.

Patients should be monitored for signs and symptoms of infection and treated appropriately. As appropriate, prophylactic antibiotics should be administered and surveillance testing prior to and during treatment with tisagenlecleucel should be employed.

Institutional guidelines for vaccination (e.g. pneumococcus) should be followed before starting tisagenlecleucel therapy. As the lack of effective B cells after infusion makes the likelihood of a systemic infection considerable, vaccination with live virus vaccines should not be given for at least 6 weeks prior to the start of lymphodepleting chemotherapy, during tisagenlecleucel and until immune recovery following treatment with tisagenlecleucel.

Any suspected cases of viral hepatitis or HIV should be referred to a specialist.

In patients with low immunoglobulin levels preventive measures such as immunoglobulin replacement and rapid attention to signs and symptoms of infection should be implemented as per age and local specific guidelines.

6.6.2.6 Febrile neutropenia

Febrile neutropenia (significantly decreased neutrophil count with fever) may develop in the course of chemotherapy (including lymphodepletion) and may be concurrent with CRS. A febrile participant should be evaluated for infection ([Section 4.5.1.5](#)) and CRS ([Section 4.5.1.1](#)) and managed appropriately with fluids, antibiotics, and supportive care, if applicable.

In the event that the patient develops sepsis or systemic bacteremia following tisagenlecleucel cell infusion, appropriate cultures and medical management should be initiated. If a

contaminated tisagenlecleucel cell product is suspected, the product can be retested for sterility using archived samples that are stored at the manufacturing site.

6.6.2.7 B cell depletion and/ or hypogammaglobulinemia

Monitor immunoglobulin levels after treatment with tisagenlecleucel, use infection precautions including antibiotic prophylaxis and immunoglobulin replacement as appropriate and per local standard of care.

In case of new or worsening symptoms suggestive of PML, consultation with a neurologist should be considered.

6.6.2.8 Hematopoietic cytopenias not resolved by day 28 post infusion

Since myeloid growth factors, particularly granulocyte macrophage colony stimulating factor (GM-CSF), have the potential to worsen CRS (if it occurs), these are not recommended during the first 3 weeks after tisagenlecleucel infusion or until CRS has resolved.

Haematopoietic cytopenias should be managed with standard measures of observation, blood product support growth factors and/or antibiotics as indicated and per local standard of care.

6.6.2.9 Replication competent lentivirus (RCL) production

The lentiviral vector has been designed to minimize the probability non-homologous recombination, thereby preventing the generation of a RCL, however, this remains a theoretical possibility. It will be detected by blood specimen, e.g., using Vesicular Stomatitis Virus/Glycoprotein (VSV-G) quantitative PCR. If a positive RCL assay result is obtained from a participant, the Investigator will be informed and the participant rescheduled for a retest of the DNA test. If blood samples for RCL testing are negative through Month 12, all samples taken after Month 12 may be stored for potential future testing.

Currently, it is not known, how to manage a participant with confirmed RCL and, therefore, should be addressed on a case by case basis. Some considerations are:

- Intensive follow-up of the participant in consultation with gene therapy experts, study investigators, and Health Authorities
- Inform local and country specific public health officials
- Identify sexual partners and provide appropriate counseling and intervention

6.6.2.10 Secondary malignancies including vector insertion site oligo/monoclonality)

All secondary malignancy should be managed/treated according to current medical practice and local standard of care.

For the follow-up of secondary malignancy, refer to [Section 10.2.6](#).

6.6.3 Emergency breaking of assigned treatment code

Since this is an open label study, this is not applicable.



6.7 Preparation and dispensation

For further preparation and administration of tisagenlecleucel, please refer to the [\[Investigational Product Handling Manual\]](#).

SOC immunochemotherapy should be handled as per local institutional guidance.

6.7.1 Handling of study treatment and additional treatment

6.7.1.1 Handling of tisagenlecleucel

Study treatment must be received by a designated person at the study site, handled and stored safely and properly and kept in a secured location to which only the investigator and designated site personnel have access. Upon receipt, all study treatment must be stored according to the instructions specified on the labels and in the [Tisagenlecleucel Investigator's Brochure]. Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis CO Quality Assurance.

For more details please refer to [\[Investigational Product Handling Manual\]](#).

Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the study treatment but no information about the participant except for the medication number.

The investigator must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Monitoring of drug accountability will be performed by monitors during site visits or remotely and at the completion of the trial.

6.7.1.2 Tisagenlecleucel disposal and destruction

Tisagenlecleucel may require disposal for a variety of reasons, including but not limited to: 1) Mislabeled product; 2) Condition of patient prohibits infusion, and/or 3) Patient refuses infusion. Disposal of unused tisagenlecleucel must be approved by Novartis global study team. Upon Novartis's approval, tisagenlecleucel may be disposed of according to local laws/ institutional SOP. Any used infusion supplies, including the infusion bag(s) and tubing, must be disposed of according to local institutional biosafety standard operating procedures. For further details, please refer to the specific guidance provided in the [\[Investigational Product Handling Manual\]](#). Reconciliation of tisagenlecleucel shipped, administered, and remaining, is performed by Novartis (or designee). All tisagenlecleucel dispositions will be documented in the study files. At study close-out, and, as appropriate during the course of the study, the investigator will return a copy of the completed drug accountability log to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

6.7.1.3 Handling of Standard of Standard of Care Therapy, Optional Bridging Chemotherapy, and Lymphodepleting Chemotherapy

SOC therapy, optional bridging chemotherapy, and lymphodepleting chemotherapy should be handled and stored according to local guidelines and locally approved labels. The investigator must maintain an accurate record of dispensing of study treatment in a drug accountability log.



Monitoring of drug accountability will be performed by monitors during site visits or remotely and at the completion of the trial.

7 Informed consent procedures

Eligible participants may only be included in the study after providing (witnessed, where required by law or regulation), Institutional Review Board (IRB)/Independent Ethics Committee (IEC)-approved informed consent.

If applicable, in cases where the patient's representative(s) gives consent (if allowed according to local requirements), the patient must be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she must indicate agreement by personally signing and dating the written informed consent document.

Informed consent must be obtained before conducting any study-specific procedures (e.g. all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the participant source documents.

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the International Council on Harmonization (ICH) GCP guidelines and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed by Novartis before submission to the IRB/IEC.

Information about common adverse effects already known about the investigational drug can be found in the Investigator's Brochure (IB) and the core data sheet (CDS) for marketed drugs. This information will be included in the participant informed consent and should be discussed with the participant during the study as needed. Any new information regarding the safety profile of the investigational drug that is identified between IB updates will be communicated as appropriate, for example, via an investigator notification (IN) or an aggregate safety finding. New information might require an update to the informed consent and then must be discussed with the participant.

Women of child bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirements.

Male participants must be informed that if a female partner becomes pregnant while he is enrolled in the study, contact with the female partner will be attempted to request her consent to collect pregnancy outcome information.

A copy of the approved version of all consent forms must be provided to Novartis/sponsor after IRB/IEC approval.

8 Visit schedule and assessments

Four tables will be used to manage assessments for the entire study duration

- Visit evaluation schedule from pre-screening to randomization ([Table 8-1](#))
- Visit evaluation schedule for Arm A ([Table 8-2](#))

- Visit evaluation schedule for Arm B (Table 8-3)
- Visit evaluation schedule for patient who cross over from Arm B to Arm A (Table 8-4)

Participants should be seen for all visits/assessments as outlined in the assessment schedule or as close to the designated day/time as possible.

During the 1st month following tisagenlecleucel infusion, patients will undergo assessments as per Table 8-2 or Table 8-4. If requested by HA or EC/IRB or based on local practice, more frequent monitoring assessments can be implemented by the physicians. Visits denoted with an asterisk (*) are timed based on a specific study treatment (chemotherapy cycles, tisagenlecleucel, or HSCT). All visits without an asterisk are timed based on the date of randomization.

Missed or rescheduled visits should not lead to automatic discontinuation. Participants who prematurely discontinue the study for any reason should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the Month 60/EOT visit will be performed. At this Month 60/EOT visit, all dispensed investigational product should be reconciled, and the adverse events and concomitant medications recorded on the CRF.

Patients who received tisagenlecleucel and who discontinue from the primary follow up due to BIRC-confirmed PD/SD prior to Month 60 will be followed every 3 months until month 12, then every 6 months until month 24, then yearly until month 60 in order to collect key safety data up to 5 years as part of long term additional follow-up. In cases where a patient discontinues without BIRC confirmed PD/SD, it may be possible for the patient to be followed for only key safety follow-up (without efficacy assessments) only after consultation and documented agreement with the Novartis medical monitor.

All randomized patients should be followed-up for survival every 3 months until the end of study (defined as the last visit for the last patient randomized). If a patient misses a quarterly scheduled visit where survival status is required, or if the time-point does not align with a scheduled visit, survival status can be obtained via phone contact.

After 5 years, the patients who received tisagenlecleucel will continue to be followed for safety in a separate long-term follow-up (LTFU) study, [CCTL019A2205B].

In each table, required assessments are indicated with an “X” at the visits when they are performed. The letter (D) under the category column indicates the assessments that will have data entered into the clinical database and (S) is for assessments that will have data remain as source documentation. All data obtained from these assessments must be supported in the patient’s source documentation.

No CRF will be used in the patient’s source documentation.



Table 8-1 Visit evaluation schedule pre-screening to randomization

Phase: Screening to Randomization	Category	Protocol Section	Pre-Screening	Screening	Randomization
Visit					
Study day				D-14 to -1 (± 7d)	Day 1
Identify Patient	S	8.1.	X		
Confirm Slot Availability	S	8.1.	X		
Obtain Informed Consent	D	7.		X	
IRT Registration	S	6.3.1.		X	X
Randomization by IRT	D	6.3.2.			X
Stratification by IRT	D	6.3.2.			X
Demography	D	8.2.		X	
Inclusion/exclusion criteria	D	5.		X	
Medical history	D	8.2.		X	
Diagnosis and Extent of Cancer	D	8.2.		X	
Prior antineoplastic therapy	D	16.3.		X	
Prior/concomitant medications	D	6.2.1.		X	X
Tumor Biopsy (CD19, tumor subtype, gene expression, PD1, PD-L1, Ki67, t(14;18), bcl-2, bcl-6, c-myc) ¹	D	8.5.3.		X	
Physical examination	S	8.4.		X	
Performance status	D	8.4.		X	
Prognostic score (IPI)	D	6.3.2.		X	
Height	D	8.4.		X	
Weight	D	8.4.		X	
Vital signs	D	8.4.		X	
Pulse oximetry	D	8.4.		X	
Spirometry	S	8.4.4.		X(allowed up to 4 weeks prior to randomization)	

Phase: Screening to Randomization	Category	Protocol Section	Pre-Screening	Screening	Randomization
Visit					
Study day				D-14 to -1 (± 7d)	Day 1
ECHO/MRA/MUGA	D	8.4.2.1.		X (allowed up to 4 weeks prior to randomization)	
Electrocardiogram (ECG)	D	8.4.2.		X (allowed up to 4 weeks prior to randomization)	
Leukapheresis	D	8.1.		X	
PET-CT with contrast enhanced diagnostic (Dx) CT – Neck, Chest, Abdomen, Pelvis	D	8.3.		X (allowed up to 4 weeks prior to randomization)	
CT/MRI – Neck, Chest, Abdomen, Pelvis	D	8.3.		X If no Dx PET-CT	
Dedicated FDG-PET	D	8.3.		X If no PET-CT	
CT/MRI Brain and/or CSF cytology by Lumbar Puncture	D	8.3.		X (allowed up to 4 weeks prior to randomization)	
Response evaluation per Lugano classification 2014	D	16.2.		X	
Bone marrow biopsy and/ or aspirate	D	8.3.		X (allowed up to 4 weeks prior to randomization)	
Adverse events	D	10.1.1		X	X
Pregnancy Reporting	S	10.1.5		X	X ⁴
Fertility Assessment	S	8.4.3		X	
Central Hematology	D	8.4.1		X	
Central Chemistry	D	8.4.1.		X	
Central Cardiac Enzymes	D	8.4.1.		X	
Flow cytometry (leukapheresis product) – Local assessment	D	8.4.1.		X	
Serum or Urine pregnancy test	S	8.4.1.		X (Serum) pre-leukapheresis	
Viral serology (EBV, HIV, HBsAg, HBsAb, HBeAb, HCVab)	D	8.4.1.		X	

Phase: Screening to Randomization	Category	Protocol Section	Pre-Screening	Screening	Randomization
Visit					
Study day				D-14 to -1 (± 7d)	Day 1
Central Coagulation (PT, aPTT, INR, fibrinogen, D-dimer)	D	8.4.1.		X	
Central Serum immunoglobulin levels (IgG, IgA, IgM)	D	8.4.1.		X	
Urine Dipstick	D	8.4.1.		X	
Cytokines (serum) ³	D	8.5.2.			X ⁴
Tisagenlecleucel cellular kinetics by qPCR (PB)	D	8.5.2.			X ⁴
Humoral Immunogenicity (serum)	D	8.5.2.			X ⁴
Cellular Immunogenicity (Peripheral Blood)	D	8.5.2.			X ⁴
Immunophenotyping, Ig deep sequencing. gene expression ²	D	8.5.3.		X (peripheral blood before leukapheresis and leukapheresis sample)	X ⁴ (peripheral blood)
Peripheral blood (cell levels- central assessment) ³	D	8.5.3.		X	X ⁴
RCL by VSV-g q-PCR	D	8.4.5.			X ⁴
SF-36v2 (Acute Form)	D	8.5.1.1			X ⁴
FACT-Lym	D	8.5.1.2			X ⁴
EQ-5D-5L	D	8.5.1.3			X ⁴
Healthcare resource utilization	D	8.5.1.4			X ⁴
Disposition (End of Phase)	D	8.1.1.			X
<p>1 For patients enrolled in China: Tumor biopsy will not be submitted centrally for exploratory assessments; however a tumor biopsy must be done for eligibility and screening purposes with local pathology assessment.</p> <p>2 For patients enrolled in China: This sample will not be collected.</p> <p>3 For patients enrolled in China: This sample should be collected only if approval has been obtained by all relevant Chinese authorities.</p> <p>4 Assessments required at the time of randomization may be completed at any time during the screening period as long as they occur prior to the IRT randomization call.</p>					

Table 8-2 Visit evaluation schedule for Arm A (patients randomized to tisagenlecleucel treatment strategy)

Phase Arm A			Pre-tisagenlecleucel infusion				Tisagenlecleucel Treatment and Follow up																		
Visit	Category	Protocol Section	Optional Bridging Chemotherapy		Post-bridging Evaluation	Lymphodepleting Chemotherapy	Pre-tisagenlecleucel Infusion	Tisagenlecleucel Infusion	Post-tisagenlecleucel safety follow-up visits (scheduled based on tisagenlecleucel infusion date)						Safety and Efficacy Follow-up visits (scheduled based on randomization date)				End of Treatment and Primary Follow-up	Safety Follow-up Visit ³	Long term additional Follow-up ⁴	Survival Follow-up			
Study day			Repeat for each cycle ¹																						
			D1 ±3d*	D15 ±3d ^{1*}	Week 6 ± 14d ²	Infusion -7d to Infusion -3d*	Infusion-1d*	Infusion*	Infusion +1d*	Infusion +3d ±1d*	Infusion +6d ±1d*	Infusion +10d ±3d*	Infusion +13d ±3d*	Infusion +21d ±3d*	Infusion +28d ±7d*	Week 12 ±7d	M4 M5, ±14d	M6 M9 M12 ±14d	M18 ±14d	M24 M36 M48 ±14d	M60±14d	See footnote ³	Post relapse ⁴	q3M	
IRT Registration	S		X (only for first cycle)		X	X		X								X					X				
Concomitant Treatments																									
Concomitant medications	D	16.3.	Continuous until 8 weeks after last treatment administration or prior to start of new anticancer therapy, whichever comes first																				X		
Concomitant medications (modified captured)	D	16.3.														For patients that receive tisagenlecleucel, starting 8 weeks after tisagenlecleucel or prior to start of new anticancer therapy, whichever comes first						X			

Phase Arm A			Pre-tisagenlecleucel infusion					Tisagenlecleucel Treatment and Follow up																	
Visit	Category	Protocol Section	Optional Bridging Chemotherapy	Post-bridging Evaluation		Lymphodepleting Chemotherapy	Pre-tisagenlecleucel Infusion	Tisagenlecleucel Infusion	Post-tisagenlecleucel safety follow-up visits (scheduled based on tisagenlecleucel infusion date)							Safety and Efficacy Follow-up visits (scheduled based on randomization date)						End of Treatment and Primary Follow-up	Safety Follow-up Visit ³	Long term additional Follow-up ⁴	Survival Follow-up
Study day			Repeat for each cycle ¹		Week 6 ± 14d ²	Infusion -7d to Infusion -3d*	Infusion-1d*	Infusion*	Infusion +1d*	Infusion +3d ±1d*	Infusion +6d ±1d*	Infusion +10d ±3d*	Infusion +13d ±3d*	Infusion +21d ±3d*	Infusion +28d ±7d*	Week 12 ±7d	M4 M5, ±14d	M6 M9 M12 ±14d	M18 ±14d	M24 M36 M48 ±14d	M60±14d	See footnote ³	Post relapse ⁴	q3M	
		D1 ±3d*	D15 ±3d ^{1*}																						
Post-treatment Antineoplastic therapies	D	16.3.	Continuous																			X	X		
Physical Assessments																									
Physical examination	S	8.4.	X	X	X	X	X	X	X		X		X	X											
ICANS Consensus Grading & ICE score	D	4.5.1.2					X	At the first sign or symptom of neurologic toxicity, the ICANS grade should be determined (as part of or outside the scheduled physical examination). If the patient experiences suspected worsening of the event, the grade should be reassessed and the worst grade should be recorded.																	
Performance status	D	8.4.	X	X	X	X	X	X	X		X		X	X	X	X	X	X	X	X	X				
Weight	D	8.4.	X			X		X						X	X	X	X	X	X	X					

[illegible]

Phase Arm A			Pre-tisagenlecleucel infusion				Tisagenlecleucel Treatment and Follow up																	
Visit	Category	Protocol Section	Optional Bridging Chemotherapy		Post-bridging Evaluation	Lymphodepleting Chemotherapy	Pre-tisagenlecleucel Infusion	Tisagenlecleucel Infusion	Post-tisagenlecleucel safety follow-up visits (scheduled based on tisagenlecleucel infusion date)						Safety and Efficacy Follow-up visits (scheduled based on randomization date)				End of Treatment and Primary Follow-up	Safety Follow-up Visit ³	Long term additional Follow-up ⁴	Survival Follow-up		
Study day			D1 ±3d*	D15 ±3d ¹ *	Week 6 ± 14d ²	Infusion -7d to Infusion -3d*	Infusion-1d*	Infusion*	Infusion +1d*	Infusion +3d ±1d*	Infusion +6d ±1d*	Infusion +10d ±3d*	Infusion +13d ±3d*	Infusion +21d ±3d*	Infusion +28d ±7d*	Week 12 ±7d	M4 M5, ±14d	M6 M9 M12 ±14d	M18 ±14d	M24 M36 M48 ±14d	M60±14d	See footnote ³	Post relapse ⁴	q3M
Efficacy Assessments																								
PET-CT with contrast enhanced diagnostic (Dx) CT – Neck, Chest, Abdomen, Pelvis	D	8.3.			X										X		X M6 only							
CT/MRI – Neck, Chest, Abdomen, Pelvis (PET-CT with Dx CT is preferred for all image visits)	D	8.3.			X if no Dx PET-CT										X if no Dx PET-CT		X at M9, M12 (M6 only if no Dx PET-CT)	X	X	X				

Phase Arm A			Pre-tisagenlecleucel infusion					Tisagenlecleucel Treatment and Follow up																		
Visit	Category	Protocol Section	Optional Bridging Chemotherapy		Post-bridging Evaluation	Lymphodepleting Chemotherapy	Pre-tisagenlecleucel Infusion	Tisagenlecleucel Infusion	Post-tisagenlecleucel safety follow-up visits (scheduled based on tisagenlecleucel infusion date)							Safety and Efficacy Follow-up visits (scheduled based on randomization date)							End of Treatment and Primary Follow-up	Safety Follow-up Visit ³	Long term additional Follow-up ⁴	Survival Follow-up
Study day			Repeat for each cycle ¹		Week 6 ± 14d ²	Infusion -7d to Infusion -3d*	Infusion-1d*	Infusion*	Infusion +1d*	Infusion +3d ±1d*	Infusion +6d ±1d*	Infusion +10d ±3d*	Infusion +13d ±3d*	Infusion +21d ±3d*	Infusion +28d ±7d*	Week 12 ±7d	M4 M5, ±14d	M6 M9 M12 ±14d	M18 ±14d	M24 M36 M48 ±14d	M60±14d	See footnote ³	Post relapse ⁴	q3M		
			D1 ±3d*	D15 ±3d1*																						
Dedicated FDG-PET	D	8.3.			X if no PET-CT											X if no PET-CT		M6 only if no PET-CT								
Response evaluation per Lugano classification 2014	D	16.2.			X											X		X	X	X						
Response (CR) confirmation by PET-CT or dedicated FDG-PET	D	8.3.			Only for new CR and not previously documented																					
Bone marrow biopsy and/or aspirate for efficacy	D	8.3.			Only if prior history of BM involvement to confirm CR																					
CT/MRI Brain and/or CSF cytology by lumbar puncture	D	8.3.			As clinically indicated																					

Phase Arm A			Pre-tisagenlecleucel infusion					Tisagenlecleucel Treatment and Follow up																				
Visit	Category	Protocol Section	Optional Bridging Chemotherapy		Post-bridging Evaluation		Lymphodepleting Chemotherapy	Pre-tisagenlecleucel Infusion	Tisagenlecleucel Infusion	Post-tisagenlecleucel safety follow-up visits (scheduled based on tisagenlecleucel infusion date)							Safety and Efficacy Follow-up visits (scheduled based on randomization date)							End of Treatment and Primary Follow-up	Safety Follow-up Visit ³	Long term additional Follow-up ⁴	Survival Follow-up	
Study day			Repeat for each cycle ¹		Week 6 ± 14d ²	Infusion -7d to Infusion -3d*	Infusion-1d*	Infusion*	Infusion +1d*	Infusion +3d ±1d*	Infusion +6d ±1d*	Infusion +10d ±3d*	Infusion +13d ±3d*	Infusion +21d ±3d*	Infusion +28d ±7d*	Week 12 ±7d	M4 M5, ±14d	M6 M9 M12 ±14d	M18 ±14d	M24 M36 M48 ±14d	M60±14d	See footnote ³	Post relapse ⁴	q3M				
			D1 ±3d*	D15 ±3d ^{1*}																								
Safety assessments																												
Adverse events	D	10.1.	Continuous until 8 weeks after tisagenlecleucel or prior to start of new anticancer therapy, whichever comes first																				X					
Protocol defined AE and AESI, including new malignancies	D	16.3 .														Continuous starting 8 weeks after tisagenlecleucel or prior to start of new anticancer therapy, whichever comes first						X	X					
Pregnancy Reporting	S	10.1.5	Continuous																							X	X	
Laboratory assessments																												
Central Hematology	D	8.4.1.	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X					
Central Chemistry	D	8.4.1.	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X						
Central Cardiac Enzymes	D	8.4.1.	As clinically indicated																									

[illegible]

Phase Arm A			Pre-tisagenlecleucel infusion				Tisagenlecleucel Treatment and Follow up																	
Visit	Category	Protocol Section	Optional Bridging Chemotherapy		Post-bridging Evaluation	Lymphodepleting Chemotherapy	Pre-tisagenlecleucel Infusion	Tisagenlecleucel Infusion	Post-tisagenlecleucel safety follow-up visits (scheduled based on tisagenlecleucel infusion date)							Safety and Efficacy Follow-up visits (scheduled based on randomization date)					End of Treatment and Primary Follow-up	Safety Follow-up Visit ³	Long term additional Follow-up ⁴	Survival Follow-up
Study day			Repeat for each cycle ¹		Week 6 ± 14d ²	Infusion -7d to Infusion -3d*	Infusion-1d*	Infusion*	Infusion +1d*	Infusion +3d ±1d*	Infusion +6d ±1d*	Infusion +10d ±3d*	Infusion +13d ±3d*	Infusion +21d ±3d*	Infusion +28d ±7d*	Week 12 ±7d	M4 M5, ±14d	M6 M9 M12 ±14d	M18 ±14d	M24 M36 M48 ±14d	M60±14d	See footnote ³	Post relapse ⁴	q3M
			D1 ±3d*	D15 ±3d ^{1*}																				
Urine Dipstick	D	8.4.1.	X only first cycle			X		X																
Tisagenlecleucel cellular kinetics, biomarker and safety assessments																								
Cytokines (serum) ⁵	D	8.5.2.				X	X	X	X	X	X	X	X	X	X		M6 and M12							
Humoral Immunogenicity (serum)	D	8.5.2.					X						X		X		X M4 only	M6 and M12	X	M24 only	X		X until M12	
Cellular Immunogenicity (Peripheral Blood)	D	8.5.2.					X						X		X		X M4 only	M6 and M12	X	M24 only	X		X until M12	

Phase Arm A			Pre-tisagenlecleucel infusion				Tisagenlecleucel Treatment and Follow up																		
Visit	Category	Protocol Section	Optional Bridging Chemotherapy	Post-bridging Evaluation	Lymphodepleting Chemotherapy	Pre-tisagenlecleucel Infusion	Tisagenlecleucel Infusion	Post-tisagenlecleucel safety follow-up visits (scheduled based on tisagenlecleucel infusion date)						Safety and Efficacy Follow-up visits (scheduled based on randomization date)					End of Treatment and Primary Follow-up	Safety Follow-up Visit ³	Long term additional Follow-up ⁴	Survival Follow-up			
Study day			Repeat for each cycle ¹					Infusion +1d*	Infusion +3d ±1d*	Infusion +6d ±1d*	Infusion +10d ±3d*	Infusion +13d ±3d*	Infusion +21d ±3d*	Infusion +28d ±7d*	Week 12 ±7d	M4 M5, ±14d	M6 M9 M12 ±14d	M18 ±14d	M24 M36 M48 ±14d	M60±14d	See footnote ³	Post relapse ⁴	q3M		
CRS assessments in peripheral blood (serum cytokines, inflammatory markers, tisagenlecleucel cellular kinetics) ⁵	D	8.5.2.						As clinically indicated depending upon the presence and time-course of CRS and administration of anti-cytokine therapies: For tisagenlecleucel cellular kinetics, refer to Table 8-12 . (qPCR in peripheral blood) and Table 8-13 (flow in peripheral blood). For biomarkers refer to Table 8-19 .																	
Tisagenlecleucel, cytokines, inflammatory markers assessments in PB in patients treated with tocilizumab ⁵	D	8.5.2.						For qPCR cellular kinetics, please refer to Table 8-18 , and for inflammatory biomarkers, please refer to Table 8-19																	
Tisagenlecleucel cellular kinetics by qPCR (PB)	D	8.5.2.					X pre-infusion	X	X	X	X	X	X	X	X	X M4 only	X	X	X	X					

Phase Arm A			Pre-tisagenlecleucel infusion				Tisagenlecleucel Treatment and Follow up																		
Visit	Category	Protocol Section	Optional Bridging Chemotherapy	Post-bridging Evaluation	Lymphodepleting Chemotherapy	Pre-tisagenlecleucel Infusion	Tisagenlecleucel Infusion	Post-tisagenlecleucel safety follow-up visits (scheduled based on tisagenlecleucel infusion date)								Safety and Efficacy Follow-up visits (scheduled based on randomization date)				End of Treatment and Primary Follow-up	Safety Follow-up Visit ³	Long term additional Follow-up ⁴	Survival Follow-up		
Study day			Repeat for each cycle ¹		Week 6 ± 14d ²	Infusion -7d to Infusion -3d*	Infusion -1d*	Infusion*	Infusion +1d*	Infusion +3d ±1d*	Infusion +6d ±1d*	Infusion +10d ±3d*	Infusion +13d ±3d*	Infusion +21d ±3d*	Infusion +28d ±7d*	Week 12 ±7d	M4 M5, ±14d	M6 M9 M12 ±14d	M18 ±14d	M24 M36 M48 ±14d	M60±14d	See footnote ³	Post relapse ⁴	q3M	
D1 ±3d*	D15 ±3d ^{1*}																								
Tisagenlecleucel cellular kinetics by flow cytometry (Peripheral Blood) ⁵	D	8.5.2.										X			X	X									
Tumor biopsy (CD19 expression, PD1, PDL1, IDO1, gene expression profiling) ⁶	D	8.5.3.							Per sampling schedule in Table 8-22 and at relapse and progression if accessible and does not impact treatment																
Tisagenlecleucel cellular kinetics Bone Marrow (qPCR)	D	8.5.2.														X	As clinically indicated								
Tisagenlecleucel cellular kinetics – CSF (q-PCR)	D	8.5.2.						As clinically indicated																	

Phase Arm A			Pre-tisagenlecleucel infusion				Tisagenlecleucel Treatment and Follow up																	
Visit	Category	Protocol Section	Optional Bridging Chemotherapy		Post-bridging Evaluation	Lymphodepleting Chemotherapy	Pre-tisagenlecleucel Infusion	Tisagenlecleucel Infusion	Post-tisagenlecleucel safety follow-up visits (scheduled based on tisagenlecleucel infusion date)						Safety and Efficacy Follow-up visits (scheduled based on randomization date)					End of Treatment and Primary Follow-up	Safety Follow-up Visit ³	Long term additional Follow-up ⁴	Survival Follow-up	
Study day			D1 ±3d*	D15 ±3d ¹ *	Week 6 ± 14d ²	Infusion -7d to Infusion -3d*	Infusion-1d*	Infusion*	Infusion +1d*	Infusion +3d ±1d*	Infusion +6d ±1d*	Infusion +10d ±3d*	Infusion +13d ±3d*	Infusion +21d ±3d*	Infusion +28d ±7d*	Week 12 ±7d	M4 M5, ±14d	M6 M9 M12 ±14d	M18 ±14d	M24 M36 M48 ±14d	M60±14d	See footnote ³	Post relapse ⁴	q3M
Immunophenotyping, Ig deep sequencing, gene expression-Peripheral Blood ⁶	D	8.5.3.				X	X				X	X			X	X		X	X	X	X			
Peripheral blood (B and T cell levels- central assessment) ⁵	D	8.5.3.				X	X				X	X	X			X		M6 and M12	X	X	X		X	
RCL by VSV-g q- PCR	D	8.4.5.				X										X		X	X	X	X		X	
Tisagenlecleucel cell product sample for correlative studies ⁶	D	8.5.3.				X																		
Electronic Patient Reported Outcomes																								
SF-36v2 (Acute Form)	D	8.5.1.1			X											X		X	X	X	X ⁷		X ⁷	
EQ-5D-5L	D	8.5.1.3			X											X		X	X	X	X ⁷		X ⁷	

Phase Arm A			Pre-tisagenlecleucel infusion				Tisagenlecleucel Treatment and Follow up																		
Visit	Category	Protocol Section	Optional Bridging Chemotherapy	Post-bridging Evaluation	Lymphodepleting Chemotherapy	Pre-tisagenlecleucel Infusion	Tisagenlecleucel Infusion	Post-tisagenlecleucel safety follow-up visits (scheduled based on tisagenlecleucel infusion date)						Safety and Efficacy Follow-up visits (scheduled based on randomization date)				End of Treatment and Primary Follow-up	Safety Follow-up Visit ³	Long term additional Follow-up ⁴	Survival Follow-up				
Study day			Repeat for each cycle ¹		Week 6 ± 14d ²	Infusion -7d to Infusion -3d*	Infusion-1d*	Infusion*	Infusion +1d*	Infusion +3d ±1d*	Infusion +6d ±1d*	Infusion +10d ±3d*	Infusion +13d ±3d*	Infusion +21d ±3d*	Infusion +28d ±7d*	Week 12 ±7d	M4 M5, ±14d	M6 M9 M12 ±14d	M18 ±14d	M24 M36 M48 ±14d	M60±14d	See footnote ³	Post relapse ⁴	q3M	
			D1 ±3d*	D15 ±3d ^{1*}																					
FACT-Lym	D	8.5.1.2			X											X		X	X	X	X ⁷		X ⁷		
Healthcare resource utilization	D	8.5.1.4	Continuous until Month 6																						
Survival Follow-up	D	8.5.5	For all randomized patients, follow-up for survival every 3 months until the end of study (defined as the last visit for the last patient randomized). If a patient misses a quarterly scheduled visit where survival status is required, or if the time-point does not align with a scheduled visit, survival status can be obtained via phone contact																						
Disposition (End of Phase)	D	9.1.2.																			X		X		
1 For patients receiving R-GemOx bridging therapy, 14 day cycles will be used. Day 1 assessments specified in the VES are to occur on Day 1 of odd-numbered cycles (i.e. C1D1, C3D1, C5D1, etc.), and Day 15 assessments specified in the VES are to occur on Day 1 of even-numbered cycles (i.e. C2D1, C4D1, C6D1, etc.). For patients receiving R-GDP Day 15 assessments may be performed on Day 8 on the day of gemcitabine dosing.																									
2 The Week 6 visit should be scheduled after the completion of all planned bridging chemotherapy and as close as possible before lymphodepleting chemotherapy while staying within the visit window.																									
3 The safety follow-up visit should occur 8 weeks after last treatment administration or prior to starting new anticancer therapy, whichever occurs first. After this safety visit occurs, adverse events and concomitant medications will follow a modified reporting criteria in patients that receive tisagenlecleucel (Section 16.3 Appendix 3). For ease of scheduling, the safety follow-up visit can occur as late as 9 weeks from their last treatment administration.																									

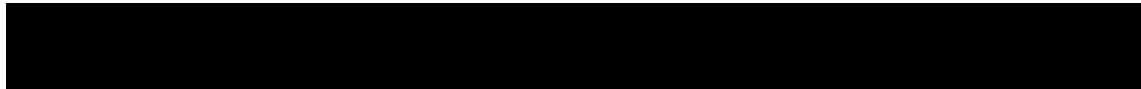
Phase Arm A			Pre-tisagenlecleucel infusion				Tisagenlecleucel Treatment and Follow up																	
Visit	Category	Protocol Section	Optional Bridging Chemotherapy		Post-bridging Evaluation	Lymphodepleting Chemotherapy	Pre-tisagenlecleucel Infusion	Tisagenlecleucel Infusion	Post-tisagenlecleucel safety follow-up visits (scheduled based on tisagenlecleucel infusion date)						Safety and Efficacy Follow-up visits (scheduled based on randomization date)				End of Treatment and Primary Follow-up	Safety Follow-up Visit ³	Long term additional Follow-up ⁴	Survival Follow-up		
Study day			D1 ±3d*	D15 ±3d ^{1*}	Week 6 ± 14d ²	Infusion -7d to Infusion -3d*	Infusion-1d*	Infusion*	Infusion +1d*	Infusion +3d ±1d*	Infusion +6d ±1d*	Infusion +10d ±3d*	Infusion +13d ±3d*	Infusion +21d ±3d*	Infusion +28d ±7d*	Week 12 ±7d	M4 M5, ±14d	M6 M9 M12 ±14d	M18 ±14d	M24 M36 M48 ±14d	M60±14d	See footnote ³	Post relapse ⁴	q3M
4 Patients that receive tisagenlecleucel and have BIRC-confirmed PD/SD prior to Month 60 will be followed to collect key safety data every 3 months until M12, then every 6 months until M24, then yearly until M60. All visits may occur ±14 days.																								
5 For patients enrolled in China: This sample should be collected only if approval has been obtained by all relevant Chinese authorities.																								
6 For patients enrolled in China: This sample will not be collected.																								
7 Patients that experience BIRC-confirmed PD/SD prior to Month 60 should complete PROs at the end of treatment visit, 4 weeks after PD/SD ±7 days , 12 weeks after PD/SD ±14 days, and 6 months after PD/SD ±14 days. If these timepoints align with scheduled long term additional follow-up visits they may be completed at the same time.																								
* Visits denoted with an asterisk should be completed based on the timing of study treatment administration. All other visits are completed based on the randomization date.																								

Table 8-3 Visit evaluation schedule for Arm B (patients randomized to SOC treatment strategy)

Phase Arm B			Treatment and Follow up															
Visit	Category	Protocol Section	SOC Treatment visits – Repeat for each cycle		HSCT visits (only required in patients that receive HSCT)			SOC Safety and Efficacy Follow-up visits (scheduled based on randomization date)							End of Treatment and Primary Follow-up	Crossover	Safety Follow-up Visit ³	Survival Follow-up
Study day			D1 ±3d*	D15 ±3d ¹ *	Conditioning Therapy start*	HSCT Day 1*	Days 7,14,21,28 post HSCT ±3d *	Week 6 ² ±14d	Week12 ±7d	M4 M5 ±14d	M6 M9 M12 ±14d	M18 ±14d	M24 M36 M48 ±14d	M60 ±14d	Week 12 ±7d onwards	See footnote ³	q3M	
IRT Registration	S		X (only first cycle)			X		X	X					X	X			
Concomitant Treatments																		
Concomitant medications	D	16.3.	Continuous until 8 weeks after the last dose of SOC study treatment or prior to start of other new anticancer therapy, whichever comes first												X	X		
Post-Treatment Antineoplastic therapies	D	16.3.	Continuous														X	
Physical Assessments																		
Physical examination	S	8.4.	X	X	X	X	X	X	X	X	X	X	X	X	X			
Performance status	D	8.4.	X	X	X	X	X	X	X	X	X	X	X	X	X			
Weight	D	8.4.	X		X				X	X	X	X	X	X				
Vital signs	D	8.4.	X	X	X	X	X	X	X	X	X	X	X	X				
ECG	D	8.4.2.	As clinically indicated													X		
ECHO/MRA/MUGA	D	8.4.2.	As clinically indicated													X		

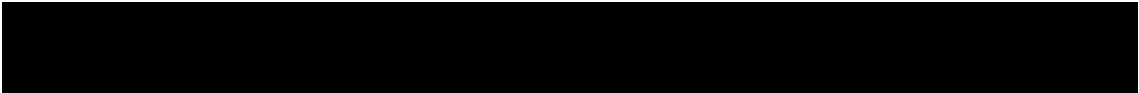
Phase Arm B			Treatment and Follow up														
Visit	Category	Protocol Section	SOC Treatment visits – Repeat for each cycle		HSCT visits (only required in patients that receive HSCT)			SOC Safety and Efficacy Follow-up visits (scheduled based on randomization date)						End of Treatment and Primary Follow- up	Crossover	Safety Follow-up Visit ³	Survival Follow-up
Study day			D1 ±3d*	D15 ±3d ¹ *	Conditioning Therapy start*	HSCT Day 1*	Days 7,14,21,28 post HSCT ±3d *	Week 6 ² ±14d	Week12 ±7d	M4 M5 ±14d	M6 M9 M12 ±14d	M18 ±14d	M24 M36 M48 ±14d	M60 ±14d	Week 12 ±7d onwards	See footnote ³	q3M
Intervention																	
Chemotherapy	D	6.1.1.	SOC treatment at the investigator's discretion														
confirm patient eligibility for crossover	D	8.3.3.													X		
Efficacy Assessments																	
PET-CT with contrast enhanced diagnostic (Dx) CT – Neck, Chest, Abdomen, Pelvis	D	8.3.						X	X		X M6 only						
CT/MRI – Neck, Chest, Abdomen, Pelvis	D	8.3.						X if no Dx PE T- CT	X if no Dx PET- CT		X at M9, M12(M6 only if no Dx PET- CT)	X	X	X			

Phase Arm B			Treatment and Follow up														
Visit	Category	Protocol Section	SOC Treatment visits – Repeat for each cycle		HSCT visits (only required in patients that receive HSCT)			SOC Safety and Efficacy Follow-up visits (scheduled based on randomization date)						End of Treatment and Primary Follow- up	Crossover	Safety Follow-up Visit ³	Survival Follow-up
Study day			D1 ±3d*	D15 ±3d ¹ *	Conditioning Therapy start*	HSCT Day 1*	Days 7,14,21,28 post HSCT ±3d *	Week 6 ² ±14d	Week12 ±7d	M4 M5 ±14d	M6 M9 M12 ±14d	M18 ±14d	M24 M36 M48 ±14d	M60 ±14d	Week 12 ±7d onwards	See footnote ³	q3M
Dedicated PET	D	8.3.						X if no PET-CT	X if no PET-CT		M6 only if no PET-CT						
Response evaluation per Lugano classification 2014	D	16.2.						X	X		X	X	X	X	X		
Response (CR) confirmation by PET-CT or PET	D	8.3.						Only for new CR and not previously documented									
CT/MRI Brain and/or CSF cytology by lumbar puncture	S	8.3.	As clinically indicated														
Bone marrow biopsy and/or aspirate	D	8.3.						Only if prior history of BM involvement to confirm CR on PET-CT or PET									
Safety Assessments																	
Adverse events	D	10.1.1.	Continuous until 8 weeks after the last dose of SOC study treatment or prior to start of other new anticancer therapy, whichever comes first													X	
Pregnancy Reporting	S	10.1.5	Continuous													X	



Phase Arm B			Treatment and Follow up															
Visit	Category	Protocol Section	SOC Treatment visits – Repeat for each cycle		HSCT visits (only required in patients that receive HSCT)			SOC Safety and Efficacy Follow-up visits (scheduled based on randomization date)							End of Treatment and Primary Follow- up	Crossover	Safety Follow-up Visit ³	Survival Follow-up
Study day			D1 ±3d*	D15 ±3d ^{1*}	Conditioning Therapy start*	HSCT Day 1*	Days 7,14,21,28 post HSCT ±3d *	Week 6 ² ±14d	Week12 ±7d	M4 M5 ±14d	M6 M9 M12 ±14d	M18 ±14d	M24 M36 M48 ±14d	M60 ±14d	Week 12 ±7d onwards	See footnote ³	q3M	
Central Hematology	D	8.4.1.	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Central Chemistry	D	8.4.1.	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Central Cardiac Enzymes	D	8.4.1.	As clinically indicated												X			
Serum or Urine pregnancy test	S	8.4.1.	X serum		X serum			X (monthly testing between visits for as long as contraception is required per local label, See Section 5.2)						X serum				
Viral serology (EBV, HIV, HBsAg, HBsAb HBcAb, HCVab)															X			
Coagulation (PT, aPTT, INR, fibrinogen, D-dimer)	D	8.4.1.	X		X				X	X						X		
Serum immunoglobulin levels (IgG, IgA, IgM)	D	8.4.1.							X	X	X							
Urine Dipstick	D	8.4.1.	X only first cycle	Repeat urinalysis following local labeling of SOC and local medical practice														
Biomarker assessments																		

Phase Arm B			Treatment and Follow up														
Visit	Category	Protocol Section	SOC Treatment visits – Repeat for each cycle		HSCT visits (only required in patients that receive HSCT)			SOC Safety and Efficacy Follow-up visits (scheduled based on randomization date)						End of Treatment and Primary Follow- up	Crossover	Safety Follow-up Visit ³	Survival Follow-up
Study day			D1 ±3d*	D15 ±3d1*	Conditioning Therapy start*	HSCT Day 1*	Days 7, 14, 21, 28 post HSCT ±3d *	Week 6 ² ±14d	Week12 ±7d	M4 M5 ±14d	M6 M9 M12 ±14d	M18 ±14d	M24 M36 M48 ±14d	M60 ±14d	Week 12 ±7d onwards	See footnote ³	q3M
Peripheral blood (B and T cell levels) ⁴	D	8.5.3							X		X (M6 and M12 only)	X	X	X			
Electronic Patient Reported Outcomes																	
SF-36v2 (Acute Form)	D	8.5.1.1						X	X		X	X	X	X ⁵	X		
EQ-5D-5L	D	8.5.1.3						X	X		X	X	X	X ⁵	X		
FACT-Lym	D	8.5.1.2.						X	X		X	X	X	X ⁵	X		
Healthcare resource utilization	D	8.5.1.4	Continuous until Month 6														
Survival follow-up	D	8.5.5.	For all randomized patients, follow-up for survival every 3 months until the end of study (defined as the last visit for the last patient randomized). If a patient misses a quarterly scheduled visit where survival status is required, or if the time-point does not align with a scheduled visit, survival status can be obtained via phone contact														
Disposition (End of Phase)	D	9.1.2.												X	X		



Phase Arm B			Treatment and Follow up														
Visit	Category	Protocol Section	SOC Treatment visits – Repeat for each cycle		HSCT visits (only required in patients that receive HSCT)			SOC Safety and Efficacy Follow-up visits (scheduled based on randomization date)					End of Treatment and Primary Follow- up	Crossover	Safety Follow-up Visit ³	Survival Follow-up	
Study day			D1 ±3d*	D15 ±3d ¹ *	Conditioning Therapy start*	HSCT Day 1*	Days 7,14,21,28 post HSCT ±3d *	Week 6 ² ±14d	Week12 ±7d	M4 M5 ±14d	M6 M9 M12 ±14d	M18 ±14d	M24 M36 M48 ±14d	M60 ±14d	Week 12 ±7d onwards	See footnote ³	q3M
1 For patients receiving R-GemOx immunochemotherapy, 14 day cycles will be used. Day 1 assessments specified in the VES are to occur on Day 1 of odd-numbered cycles (i.e. C1D1, C3D1, C5D1, etc.), and Day 15 assessments specified in the VES are to occur on Day 1 of even-numbered cycles (i.e. C2D1, C4D1, C6D1, etc.). For patients receiving R-GDP Day 15 assessments may be performed on Day 8 on the day of gemcitabine dosing.																	
2. The Week 6 PET-CT should be scheduled no sooner than 14 days after the start of the second cycle of immunochemotherapy for R-DHAP, R-GDP, and R-ICE, or 7 days after the third cycle of immunochemotherapy for R-GemOx																	
3 The safety follow-up visit should occur 8 weeks after last treatment administration or prior to starting new anticancer therapy, whichever occurs first. If the patient received HSCT, this would occur 8 weeks after HSCT. After this safety visit occurs, no new adverse events or concomitant medications need to be reported. For ease of scheduling, the safety follow-up visit can occur as late as 9 weeks from their last treatment administration.																	
4 For patients enrolled in China: This sample should be collected only if approval has been obtained by all relevant Chinese authorities.																	
5 Patients that experience BIRC-confirmed PD/SD prior to Month 60, but do not plan to crossover, should complete PROs at the end of treatment visit, 4 weeks after PD/SD ±7 days , 12 weeks after PD/SD ±14 days, and 6 months after PD/SD ±14 days. Patients that plan to crossover should complete PROs at the crossover visit.																	
*Visits denoted with an asterisk should be completed based on the timing of study treatment administrations. All other visits are completed based on the randomization date.																	

Table 8-4 Visit evaluation schedule for patients who cross over from Arm B (SOC) to Arm A (tisagenlecleucel)

Phase Crossover			Pre-Tisagenlecleucel infusion					Tisagenlecleucel Treatment and Follow up																	
Visit	Category	Protocol Section	Optional Bridging Chemo		Post-bridging Evaluation	Lymphodepleting Chemotherapy	Pre-tisagenlecleucel Infusion	Tisagenlecleucel Infusion	Post-tisagenlecleucel safety follow-up visits (timed based on tisagenlecleucel infusion date)						Safety and Efficacy Follow-up visits (timed based on crossover visit date)				End of Treatment and Primary Follow-up	Safety Follow-up ³	Long term additional Follow-up ⁴	Survival Follow-up			
Study day			Repeat for each cycle		Week 6 ±14d ²	Infusion -7d to Infusion -3d*	Infusion-1d*	Infusion*	Infusion +1d*	Infusion +3d ±1d*	Infusion +6d ±1d*	Infusion +10d ±3d*	Infusion +13d ±3d*	Infusion +21d ±3d*	Infusion +28d ±7d*	Week 12 ±7d	M4 M5, ±14d	M6 M9 M12 ±14d	M18 ±14d	M24 M36 M48 ±14d	M60±14d	See footnote ³	Post relapse ⁴	q3M	
			D1 ±3d*	D15 ±3d ^{1*}					Infusion +1d*	Infusion +3d ±1d*	Infusion +6d ±1d*	Infusion +10d ±3d*	Infusion +13d ±3d*	Infusion +21d ±3d*	Infusion +28d ±7d*	Week 12 ±7d	M4 M5, ±14d	M6 M9 M12 ±14d	M18 ±14d	M24 M36 M48 ±14d	M60±14d				
IRT Registration	S		X only first cycle		X	X		X								X					X				
Concomitant Treatments																									
Concomitant medications	D	16.3.	Continuous until 8 weeks after last treatment administration or prior to start of new anticancer therapy, whichever comes first																				X		
Concomitant medications (modified captured)	D	16.3.														For patients that receive tisagenlecleucel, starting 8 weeks after tisagenlecleucel or prior to start of new anticancer therapy, whichever comes first						X			

Phase Crossover			Pre-Tisagenlecleucel infusion					Tisagenlecleucel Treatment and Follow up																	
Visit	Category	Protocol Section	Optional Bridging Chemo	Post-bridging Evaluation	Lymphodepleting Chemotherapy	Pre-tisagenlecleucel Infusion	Tisagenlecleucel Infusion	Post-tisagenlecleucel safety follow-up visits (timed based on tisagenlecleucel infusion date)								Safety and Efficacy Follow-up visits (timed based on crossover visit date)						End of Treatment and Primary Follow-up	Safety Follow-up ³	Long term additional Follow-up ⁴	Survival Follow-up
Study day			Repeat for each cycle		Week 6 ±14d ²	Infusion -7d to Infusion -3d*	Infusion-1d*	Infusion*	Infusion +1d*	Infusion +3d ±1d*	Infusion +6d ±1d*	Infusion +10d ±3d*	Infusion +13d ±3d*	Infusion +21d ±3d*	Infusion +28d ±7d*	Week 12 ±7d	M4 M5, ±14d	M6 M9 M12 ±14d	M18 ±14d	M24 M36 M48 ±14d	M60±14d	See footnote ³	Post relapse ⁴	q3M	
D1 ±3d*	D15 ±3d†*																								
Post-treatment antineoplastic therapies	D	16.3.						Continuous														X	X		
Physical Assessments																									
Physical examination	S	8.4.	X	X	X	X	X	X	X		X		X	X											
ICANS Consensus Grading & ICE score	D	4.5.1.2					X	At the first sign or symptom of neurologic toxicity, the ICANS grade should be determined (as part of or outside the scheduled physical examination). If the patient experiences suspected worsening of the event, the grade should be reassessed and the worst grade should be recorded.																	
Performance status	D	8.4.	X	X	X	X	X	X	X		X		X	X	X	X	X	X	X	X	X				
Weight	D	8.4.	X			X		X							X	X	X	X	X	X					

[illegible]

Phase Crossover			Pre-Tisagenlecleucel infusion				Tisagenlecleucel Treatment and Follow up																	
Visit	Category	Protocol Section	Optional Bridging Chemo		Post-bridging Evaluation	Lymphodepleting Chemotherapy	Pre-tisagenlecleucel Infusion	Tisagenlecleucel Infusion	Post-tisagenlecleucel safety follow-up visits (timed based on tisagenlecleucel infusion date)							Safety and Efficacy Follow-up visits (timed based on crossover visit date)				End of Treatment and Primary Follow-up	Safety Follow-up ³	Long term additional Follow-up ⁴	Survival Follow-up	
Study day			Repeat for each cycle		Week 6 ±14d ²	Infusion -7d to Infusion -3d*	Infusion-1d*	Infusion*	Infusion +1d*	Infusion +3d ±1d*	Infusion +6d ±1d*	Infusion +10d ±3d*	Infusion +13d ±3d*	Infusion +21d ±3d*	Infusion +28d ±7d*	Week 12 ±7d	M4 M5, ±14d	M6 M9 M12 ±14d	M18 ±14d	M24 M36 M48 ±14d	M60±14d	See footnote ³	Post relapse ⁴	q3M
D1 ±3d*	D15 ±3d ^{1*}																							
Efficacy Assessments																								
Response evaluation per Lugano classification 2014 - Local	D	16.2.			X											X		X	X	X	X			
Safety assessments																								
Adverse events	D	10.1.	Continuous until 8 weeks after last treatment administration or prior to start of new anticancer therapy, whichever comes first																			X		
Protocol defined AE and AESI, including new malignancies	D	16.3.														For patients that receive tisagenlecleucel, starting 8 weeks after tisagenlecleucel or prior to start of new anticancer therapy, whichever comes first						X	X	

Phase Crossover			Pre-Tisagenlecleucel infusion				Tisagenlecleucel Treatment and Follow up																
Visit	Category	Protocol Section	Optional Bridging Chemo	Post-bridging Evaluation	Lymphodepleting Chemotherapy	Pre-tisagenlecleucel Infusion	Tisagenlecleucel Infusion	Post-tisagenlecleucel safety follow-up visits (timed based on tisagenlecleucel infusion date)							Safety and Efficacy Follow-up visits (timed based on crossover visit date)					End of Treatment and Primary Follow-up	Safety Follow-up ³	Long term additional Follow-up ⁴	Survival Follow-up
Study day			Repeat for each cycle					Infusion +1d*	Infusion +3d ±1d*	Infusion +6d ±1d*	Infusion +10d ±3d*	Infusion +13d ±3d*	Infusion +21d ±3d*	Infusion +28d ±7d*	Week 12 ±7d	M4 M5, ±14d	M6 M9 M12 ±14d	M18 ±14d	M24 M36 M48 ±14d	M60±14d	See footnote ³	Post relapse ⁴	q3M
Pregnancy Reporting	S	10.1.5	D1 ±3d*	D15 ±3d1*	Week 6 ±14d ²	Infusion -7d to Infusion -3d*	Infusion -1d*	Infusion*													X	X	
Laboratory assessments																							
Central Hematology	D	8.4.1.	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Central Chemistry	D	8.4.1.	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Central Cardiac Enzymes	D	8.4.1.	As clinically indicated																				
Serum or Urine pregnancy test	S	8.4.1.	X serum			X serum	X serum								X (monthly testing between visits for as long as contraception is required, See Section 5.2)					(urine) X		X (as per contraception requirements)	
Central Coagulation (PT, aPTT, INR, fibrinogen, D-dimer)	D	8.4.1.	X					X			X		X		X	X					X		

Phase Crossover			Pre-Tisagenlecleucel infusion				Tisagenlecleucel Treatment and Follow up																	
Visit	Category	Protocol Section	Optional Bridging Chemo	Post-bridging Evaluation	Lymphodepleting Chemotherapy	Pre-tisagenlecleucel Infusion	Tisagenlecleucel Infusion	Post-tisagenlecleucel safety follow-up visits (timed based on tisagenlecleucel infusion date)							Safety and Efficacy Follow-up visits (timed based on crossover visit date)					End of Treatment and Primary Follow- up	Safety Follow-up ³	Long term additional Follow-up ⁴	Survival Follow-up	
Study day			Repeat for each cycle		Week 6 ±14d ²	Infusion -7d to Infusion -3d*	Infusion-1d*	Infusion*	Infusion +1d*	Infusion +3d ±1d*	Infusion +6d ±1d*	Infusion +10d ±3d*	Infusion +13d ±3d*	Infusion +21d ±3d*	Infusion +28d ±7d*	Week 12 ±7d	M4 M5, ±14d	M6 M9 M12 ±14d	M18 ±14d	M24 M36 M48 ±14d	M60±14d	See footnote ³	Post relapse ⁴	q3M
D1 ±3d*	D15 ±3d1*																							
Central Serum immunoglobulin levels (IgG, IgA, IgM)	D	8.4.1.											X		X	X	X							
Rapid Influenza (A and B) Testing	D	8.4.1.				Within 10d to planned infusion																		
Urine Dipstick	D	8.4.1.	X (only first cycle)			X		X																
Tisagenlecleucel cellular kinetics, biomarker and safety assessments																								
Tisagenlecleucel cellular kinetics by qPCR (PB)	D	8.5.2.							X	X	X	X	X	X	X	X	X M4 only	X	X	X	X			

Phase Crossover			Pre-Tisagenlecleucel infusion				Tisagenlecleucel Treatment and Follow up																	
Visit	Category	Protocol Section	Optional Bridging Chemo	Post-bridging Evaluation	Lymphodepleting Chemotherapy	Pre-tisagenlecleucel Infusion	Tisagenlecleucel Infusion	Post-tisagenlecleucel safety follow-up visits (timed based on tisagenlecleucel infusion date)							Safety and Efficacy Follow-up visits (timed based on crossover visit date)					End of Treatment and Primary Follow-up	Safety Follow-up ³	Long term additional Follow-up ⁴	Survival Follow-up	
Study day			Repeat for each cycle					Infusion +1d*	Infusion +3d ±1d*	Infusion +6d ±1d*	Infusion +10d ±3d*	Infusion +13d ±3d*	Infusion +21d ±3d*	Infusion +28d ±7d*	Week 12 ±7d	M4 M5, ±14d	M6 M9 M12 ±14d	M18 ±14d	M24 M36 M48 ±14d	M60±14d	See footnote ³	Post relapse ⁴	q3M	
Tisagenlecleucel cellular kinetics by flow cytometry (Peripheral Blood) ⁵	D	8.5.2.									X			X	X									
Tisagenlecleucel cellular kinetics Bone Marrow (qPCR)	D	8.5.2.													X	As clinically indicated								
Tisagenlecleucel cellular kinetics – CSF (q-PCR)	D	8.5.2.					As clinically indicated																	
Cytokines (serum) ⁵	D	8.5.2.				X	X	X	X	X	X	X	X	X	X		M6 and M12							

Phase Crossover			Pre-Tisagenlecleucel infusion				Tisagenlecleucel Treatment and Follow up																		
Visit	Category	Protocol Section	Optional Bridging Chemo	Post-bridging Evaluation	Lymphodepleting Chemotherapy	Pre-tisagenlecleucel Infusion	Tisagenlecleucel Infusion	Post-tisagenlecleucel safety follow-up visits (timed based on tisagenlecleucel infusion date)							Safety and Efficacy Follow-up visits (timed based on crossover visit date)				End of Treatment and Primary Follow- up	Safety Follow-up ³	Long term additional Follow-up ⁴	Survival Follow-up			
Study day			Repeat for each cycle		Week 6 ±14d ²	Infusion -7d to Infusion -3d*	Infusion-1d*	Infusion *	Infusion +1d*	Infusion +3d ±1d*	Infusion +6d ±1d*	Infusion +10d ±3d*	Infusion +13d ±3d*	Infusion +21d ±3d*	Infusion +28d ±7d*	Week 12 ±7d	M4 M5, ±14d	M6 M9 M12 ±14d	M18 ±14d	M24 M36 M48 ±14d	M60±14d	See footnote ³	Post relapse ⁴	q3M	
		D1 ±3d*	D15 ±3d1*																						
Humoral Immunogenicity (serum)	D	8.5.2.					X						X		X		X M4 only	M6 and M12	X	M24 only	X		X until M12		
Cellular Immunogenicity (Peripheral Blood)	D	8.5.2.					X						X		X		X M4 only	M6 and M12	X	M24 only	X		X until M12		
CRS assessments in peripheral blood (serum cytokines, inflammatory markers, tisagenlecleucel cellular kinetics) ⁵	D	8.5.2.																					As clinically indicated depending upon the presence and time- course of CRS and administration of anti-cytokine therapies: For tisagenlecleucel cellular kinetics, refer to Table 8-12 (qPCR in peripheral blood) and Table 8-13 (flow in peripheral blood). For biomarkers refer to Table 8-19 .		

Phase Crossover			Pre-Tisagenlecleucel infusion				Tisagenlecleucel Treatment and Follow up																	
Visit	Category	Protocol Section	Optional Bridging Chemo	Post-bridging Evaluation	Lymphodepleting Chemotherapy	Pre-tisagenlecleucel Infusion	Tisagenlecleucel Infusion	Post-tisagenlecleucel safety follow-up visits (timed based on tisagenlecleucel infusion date)							Safety and Efficacy Follow-up visits (timed based on crossover visit date)						End of Treatment and Primary Follow-up	Safety Follow-up ³	Long term additional Follow-up ⁴	Survival Follow-up
Study day			Repeat for each cycle		Week 6 ±14d ²	Infusion -7d to Infusion -3d*	Infusion-1d*	Infusion*	Infusion +1d*	Infusion +3d ±1d*	Infusion +6d ±1d*	Infusion +10d ±3d*	Infusion +13d ±3d*	Infusion +21d ±3d*	Infusion +28d ±7d*	Week 12 ±7d	M4 M5, ±14d	M6 M9 M12 ±14d	M18 ±14d	M24 M36 M48 ±14d	M60±14d	See footnote ³	Post relapse ⁴	q3M
D1 ±3d*	D15 ±3d1*																							
Tisagenlecleucel, cytokines, and inflammatory markers assessments in PB in patients treated with tocilizumab ⁵	D	8.5.2.							For qPCR cellular kinetics, please refer to Table 8-18 , and for inflammatory biomarkers, please refer to Table 8-19															
RCL by VSV-g q-PCR	D	8.4.5.				X									X		X	X	X	X		X		
Tumor biopsy (CD19 expression, PD1, PDL1, IDO1, gene expression profiling) ⁶	D	8.5.3.							Per sampling schedule in Table 8-22 and at relapse and progression if accessible and does not impact treatment															

Phase Crossover			Pre-Tisagenlecleucel infusion				Tisagenlecleucel Treatment and Follow up																	
Visit	Category	Protocol Section	Optional Bridging Chemo	Post-bridging Evaluation	Lymphodepleting Chemotherapy	Pre-tisagenlecleucel Infusion	Tisagenlecleucel Infusion	Post-tisagenlecleucel safety follow-up visits (timed based on tisagenlecleucel infusion date)							Safety and Efficacy Follow-up visits (timed based on crossover visit date)				End of Treatment and Primary Follow- up	Safety Follow-up ³	Long term additional Follow-up ⁴	Survival Follow-up		
Study day			Repeat for each cycle		Week 6 ±14d ²	Infusion -7d to Infusion -3d*	Infusion-1d*	Infusion*	Infusion +1d*	Infusion +3d ±1d*	Infusion +6d ±1d*	Infusion +10d ±3d*	Infusion +13d ±3d*	Infusion +21d ±3d*	Infusion +28d ±7d*	Week 12 ±7d	M4 M5, ±14d	M6 M9 M12 ±14d	M18 ±14d	M24 M36 M48 ±14d	M60±14d	See footnote ³	Post relapse ⁴	q3M
Immunophenotyping, Ig deep sequencing, gene expression-Peripheral Blood ⁶	D	8.5.3.				X	X			X	X			X		X		X	X	X	X			
Peripheral blood (B cell levels- central assessment) ⁵	D	8.5.3.				X	X			X	X	X				X		M6 and M12	X	X	X		X	
Tisagenlecleucel cell product sample for correlative studies ⁶	D	8.5.3.				X																		
Electronic Patient Reported Outcomes (ePRO)																								
SF-36v2 (Acute Form)	D	8.5.1.1.			X											X		X	X	X	X	X ⁷	X ⁷	

Phase Crossover			Pre-Tisagenlecleucel infusion				Tisagenlecleucel Treatment and Follow up																	
Visit	Category	Protocol Section	Optional Bridging Chemo	Post-bridging Evaluation	Lymphodepleting Chemotherapy	Pre-tisagenlecleucel Infusion	Tisagenlecleucel Infusion	Post-tisagenlecleucel safety follow-up visits (timed based on tisagenlecleucel infusion date)							Safety and Efficacy Follow-up visits (timed based on crossover visit date)				End of Treatment and Primary Follow- up	Safety Follow-up ³	Long term additional Follow-up ⁴	Survival Follow-up		
Study day			Repeat for each cycle		Week 6 ±14d ²	Infusion -7d to Infusion -3d*	Infusion-1d*	Infusion*	Infusion +1d*	Infusion +3d ±1d*	Infusion +6d ±1d*	Infusion +10d ±3d*	Infusion +13d ±3d*	Infusion +21d ±3d*	Infusion +28d ±7d*	Week 12 ±7d	M4 M5, ±14d	M6 M9 M12 ±14d	M18 ±14d	M24 M36 M48 ±14d	M60±14d	See footnote ³	Post relapse ⁴	q3M
D1 ±3d*	D15 ±3d ¹ *																							
EQ-5D-5L	D	8.5.1.3.			X											X		X	X	X	X	X ₇	X ⁷	
FACT-Lym	D	8.5.1.2.			X											X		X	X	X	X	X ₇	X ⁷	
Healthcare resource utilization	D	8.5.1.4.	Continuous until Month 6																					
Survival Follow-up	D	9.2.	For all patients who crossover, follow-up for survival every 3 months until the end of study (defined as the last visit for the last patient randomized). If a patient misses a quarterly scheduled visit where survival status is required, or if the time-point does not align with a scheduled visit, survival status can be obtained via phone contact																					
Disposition (End of Phase)	D	9.1.2.																			X		X	

Phase Crossover			Pre-Tisagenlecleucel infusion				Tisagenlecleucel Treatment and Follow up																	
Visit	Category	Protocol Section	Optional Bridging Chemo		Post-bridging Evaluation	Lymphodepleting Chemotherapy	Pre-tisagenlecleucel Infusion	Tisagenlecleucel Infusion	Post-tisagenlecleucel safety follow-up visits (timed based on tisagenlecleucel infusion date)						Safety and Efficacy Follow-up visits (timed based on crossover visit date)				End of Treatment and Primary Follow- up	Safety Follow-up ³	Long term additional Follow-up ⁴	Survival Follow-up		
Study day			Repeat for each cycle		Week 6 ±14d ²	Infusion -7d to Infusion -3d*	Infusion-1d*	Infusion*	Infusion +1d*	Infusion +3d ±1d*	Infusion +6d ±1d*	Infusion +10d ±3d*	Infusion +13d ±3d*	Infusion +21d ±3d*	Infusion +28d ±7d*	Week 12 ±7d	M4 M5, ±14d	M6 M9 M12 ±14d	M18 ±14d	M24 M36 M48 ±14d	M60±14d	See footnote ³	Post relapse ⁴	q3M
			D1 ±3d*	D15 ±3d1*																				
1 For patients receiving R-GemOx bridging therapy, 14 day cycles will be used. Day 1 assessments specified in the VES are to occur on Day 1 of odd-numbered cycles (i.e. C1D1, C3D1, C5D1, etc.), and Day 15 assessments specified in the VES are to occur on Day 1 of even-numbered cycles (i.e. C2D1, C4D1, C6D1, etc.). For patients receiving R-GDP Day 15 assessments may be performed on Day 8 on the day of gemcitabine dosing.																								
2 In patients that crossover to Arm A, it is possible that the patient has tisagenlecleucel already available for infusion at the time of crossover due to an early manufacturing request. In this case the patient may proceed to infusion with no bridging and the Week 6 visit would occur after infusion. If tisagenlecleucel is not available at the time of crossover, the Week 6 assessment should occur after the completion of bridging chemotherapy as in Arm A.																								
3 The safety follow-up visit should occur 8 weeks after last treatment administration or prior to starting new anticancer therapy, whichever occurs first. After this safety visit occurs, adverse events and concomitant medications will follow a modified reporting criteria in patients that receive tisagenlecleucel (Section 16.3 Appendix 3). For ease of scheduling, the safety follow-up visit can occur as late as 9 weeks from their last treatment administration.																								
4 Patients that receive tisagenlecleucel and have PD/SD prior to Month 60 will be followed to collect key safety data every 3 months until M12, then every 6 months until M24, then yearly until M60. All visits may occur ±14 days.																								
5 For patients enrolled in China: This sample should be collected only if approval has been obtained by all relevant Chinese authorities.																								
6 For patients enrolled in China: This sample will not to be collected.																								
7 Patients that experience PD/SD prior to Month 60 should complete PROs at the end of treatment visit, 4 weeks after PD/SD ±7 days , 12 weeks after PD/SD ±14 days, and 6 months after PD/SD ±14 days. If these timepoints align with scheduled long term additional follow-up visits they may be completed at the same time.																								
* Visits denoted with an asterisk should be completed based on the timing of study treatment administrations. All other visits are completed based on the crossover visit date.																								

8.1 Screening

Patient identification

Prior to signing ICF, when an investigator identifies a potential patient for CCTL019H2301, the site will contact the sponsor to inquire about tisagenlecleucel manufacturing slot availability within 3-6 weeks. If there is manufacturing slot availability and the patient is deemed a candidate to start second line treatment after randomization then the site should proceed to ICF signature within 48 hours of this contact.

Screening

Patients must sign the IRB/EC approved informed consent form (ICF) before any study specific screening procedures. Screening assessments to determine eligibility should be performed as per the visit evaluation schedule detailed in [Table 8-1](#). Randomization should occur when all clinical eligibility has been completed.

Patients who have signed an informed consent will be registered in the IRT system and undergo a routine lymphoma staging workup including all screening assessment outlined in [Table 8-1](#).

The assessments below do not need to be repeated if performed in the context of the leukapheresis procedure or if performed as part of clinical routine within 4 weeks of randomization:

- a. Disease assessments: Any imaging assessments, bone marrow biopsies, or lumbar punctures already completed during the regular care of the participant within 4 weeks prior to randomization, including before signing the main study ICF, can be considered as the screening disease assessments for this study. Any imaging or disease assessments obtained after randomization cannot be considered for screening. The patient should not receive any anticancer therapy between the screening disease assessments and randomization.
- b. Cardiac and lung function evaluation: Heart imaging assessment, ECG, and spirometry if already completed during the regular care of the participant within 4 weeks prior to randomization, including before signing the main study ICF, can be considered as the screening disease assessments for this study.

If needed, laboratory parameters or other screening parameters may be retested within the screening period for an individual patient. In addition, rescreening (signing of a new ICF after initial screen failure) may be allowed under selected circumstances after discussion with the medical monitor. If a decision is taken, upon discussion with the medical monitor, to re-screen the patient after the patient initially screen failed, a new ICF will need to be signed, and the patient will be assigned a new patient ID. All required screening activities must be performed when the patient is re-screened for participation in the study. An individual patient may only be re-screened once for the study.

In the case where a safety laboratory assessment at screening outside of the range specified in the exclusion criteria, the assessment may be repeated once prior to randomization. If the repeat value remains outside of the specified ranges, the participant must be excluded from the study.

In the case of a logistical error (e.g. temperature control breach during apheresis shipping, contamination of cell culture, etc) which compromises the manufacture of a patient's tisagenlecleucel product, all screening procedures including collection of a new leukapheresis product can be repeated. In the event of a case that you feel qualifies as a logistical error, please consult with the Novartis medical monitor prior to repeating screening procedures for the patient.

Leukapheresis

Leukapheresis will be scheduled for cell procurement prior to final enrollment. It is strongly recommended to schedule leukapheresis prior to any planned chemotherapy or non-physiologic dose of steroids as an absolute T cell count (absolute lymphocyte count multiplied by the percentage of CD3 positive lymphocytes) $\leq 300/\text{mm}^3$ may result in a poor T cell collection and manufacturing failure. Female patients of childbearing potential must have a negative serum pregnancy test within 24 hours prior to the start of leukapheresis.

The leukapheresis collection should be registered in IRT.

Cryopreserved non mobilized leukapheresis products collected prior to study entry (historical) may be used for tisagenlecleucel manufacturing if collected at a certified apheresis center and if the product is acceptable for manufacturing.

For patients who undergo leukapheresis collection on study after signing ICF, the following criteria must be met prior to leukapheresis collection based on results of central labs:

1. Peripheral blood absolute lymphocyte count (ALC) $\geq 300/\mu\text{L}$ ($0.3 \times 10^9/\text{L}$) or peripheral blood absolute CD3 lymphocyte count must be $\geq 150/\mu\text{L}$
2. No active hepatitis B, hepatitis C, or HIV, as indicated in [Section 16.1 Appendix 1](#), or any additional testing as required by local authority within 30 days prior to leukapheresis collection
3. Treatments/medications should be stopped as described in the [\[Investigational Leukapheresis, Cryopreservation, and Scheduling Manual\]](#):

Following randomization to Arm A, or at the point of manufacturing request for crossover from Arm B, information on the patient's leukapheresis material including sample sentinel vials collected from leukapheresis (when available) will be sent to Novartis manufacturing separately or together with leukapheresis product. Patients who are not randomized, or patients who are randomized to Arm B and do not request manufacturing will not have their leukapheresis material or information sent to Novartis manufacturing facility. Final enrollment is defined as the point at which the patient meets all inclusion/exclusion criteria, and the patient is randomized to a treatment arm.

Please refer to the Leukapheresis Key Requirements within the most recent [\[Investigational Leukapheresis, Cryopreservation and Scheduling Manual\]](#) for more detailed instructions on optimal timing of leukapheresis collection, prohibited drugs, and the recommended procurement, handling and shipment procedures of the leukapheresis samples to the designated manufacturing facility.

8.1.1 Eligibility screening

Only following randomization will information on the patient's leukapheresis product be transferred to the Novartis designated manufacturing facility.

For sites performing the leukapheresis as part of this protocol leukapheresis can only be performed after patient consent has been obtained. At the time when manufacturing of tisagenlecleucel is required (by randomization or crossover), a Novartis designated manufacturing facility will then evaluate the patient's leukapheresis product for acceptance. The acceptance of the product will be registered in IRT by Novartis personnel.

Randomization will occur at the point at which a patient meets all inclusion/exclusion criteria as per investigator judgement and registers the call in IRT. The patient is then randomized using the same Participant Number assigned at screening by the site investigator or designated staff. Once assigned, the Participant Number must not be reused for any other patient and the Participant Number for that individual must not be changed. If a screened patient is not randomized for any reason, the specific reason will be entered into the clinical database on a disposition CRF.

At randomization, patients will be stratified by response to first line treatment (refractory or relapsed within 6 months from last dose of first line immunochemotherapy, and relapsed 6 to 12 months from last dose of first line immunochemotherapy), IPI (<2 v ≥ 2) per treating physician assessment at study entry, and region (North America vs. Rest of World) and randomized in IRT.

Novartis will supply a stratification form which must be signed and returned prior to randomization to ensure adequate documentation of stratification factors.

For detailed screening, and randomization procedures, related to the use of Interactive Response Technology (IRT), please refer to the [\[IRT User Manual\]](#).

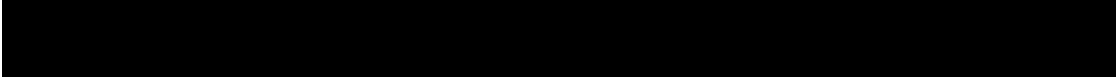
8.1.2 Information to be collected on screening failures

Participants who sign an informed consent form and subsequently found to be ineligible prior to randomization will be considered a screen failure. The reason for screen failure should be recorded on the appropriate Case Report Form. The demographic information, informed consent, leukapheresis collection information, and Inclusion/Exclusion pages must also be completed for screen failure participants. No other data will be entered into the clinical database for participants who are screen failures, unless the participant experienced a serious adverse event (see SAE section for reporting details) or an adverse event which leads to discontinuation during the screening phase. If the participant fails to be randomized, the IRT must be notified within 2 days of the screen fail that the participant was not randomized.

Participants who are randomized and fail to start treatment, e.g. participants randomized in error, will be considered an early terminator. The reason for early termination should be recorded on the appropriate Case Report Form.

8.2 Participant demographics/other baseline characteristics

Country specific regulations should be considered for the collection of demographic and baseline characteristics in alignment with CRF.



Participant demographic and baseline characteristic data are to be collected on all participants. Relevant medical history/current medical condition present before signing the informed consent will be recorded. Investigators will have the discretion to record abnormal test findings on the appropriate CRF whenever in their judgment, the test abnormality occurred prior to the informed consent signature.

8.3 Efficacy

Efficacy assessments will be performed as indicated in [Table 8-1](#), [Table 8-2](#), and [Table 8-3](#), and as clinically indicated in all randomized patients (including those who may not receive study treatment) until BIRC-confirmed SD/PD at or after week 12, death, lost to follow up or withdrawal of consent. Patients in Arm A that experience BIRC-confirmed SD/PD at or after the week 12 visit, but are still waiting to receive tisagenlecleucel (e.g. in case of remanufacturing attempt) should continue disease assessments as per local policy until SD/PD after tisagenlecleucel infusion (or until study discontinuation without infusion). These assessments will be done locally with no central review. For patients that initiate new anticancer therapy without BIRC confirmed SD/PD, efficacy assessment should be also performed just before initiation of new anticancer therapy and thereafter should continue to conduct efficacy assessments until BIRC confirmed SD/PD. For patients that are randomized to arm B and then crossover, efficacy will continue to be assessed by local investigator with no central review as per [Table 8-4](#). The crossover visit would also mark the end of the treatment and primary follow-up visit for patients in Arm B.

Efficacy evaluation will be collected as described in [Table 8-5](#) based on recommendations by the International Malignant Lymphomas Imaging Working Group ([Cheson et al 2014](#); [Barrington et al 2014](#)) and detailed in [Section 16.2 Appendix 2](#).

A BIRC appointed by Novartis will review data related to disease response assessment according to the Novartis Guideline for Efficacy Evaluation in lymphoma studies, version 2. The BIRC will review all data related to disease response for all randomized patients. Sites should request expedited review of imaging files under the conditions described in [Section 8.3.3](#). Patients who crossover to Arm A will not be assessed by BIRC. Radiological imaging will be transmitted by the sites to the imaging Contract Research Organization (CRO) designated by Novartis to undergo quality checks and central review by the BIRC. Clinical data such as, physical exam, bone marrow results, pathology/histology and cytology results; as well as, information regarding prior interventions, pre-existing radiographic findings that may mimic presence of disease at baseline/screening and on-study interventions will be transmitted to the imaging CRO for review by a medical oncologist/hematologist. At BIRC, during the overall review the available clinical data will be integrated with the pathological and radiological response data to provide the overall disease response:

The presence of one (1) or more stable, but persistent clinical lesions will downgrade a radiology CR to an overall PR.

The presence of one (1) or more new or worsening clinical lesions will result in Overall PD.

If bone marrow biopsy is not negative, a radiographic timepoint response (TPR) of CR at that time point would be downgraded to an overall PR.

A new lesion biopsy result indicating a malignancy would result in overall PD, if not already assessed as PD during the radiology review.

For any given time point, any clinical listings that are within a +14 day window (+28 day window for bone marrow data) of the radiographic time point date can be used for the corresponding oncology time point assessments. Clinical listings that are +15 days after a radiographic time point will be grouped with the next radiographic time point. For example, if the radiographic time point date is 01-Mar, and the non-bone marrow clinical evaluations on the listings occur on 10-Mar and 16-Mar, the listings from 10-Mar will be associated with the radiographic time point date of 01-Mar. The listings from 16-Mar will not be associated with the 01-Mar radiographic time point and will be grouped with the next radiographic time point. Any clinical listings that fall outside the allowable window will be evaluated with the next radiographic time point.

For bone marrow data, the assessment window will be extended to +42 days if there are no subsequent radiographic time points. This +42 day window will only apply to overall assessments associated with the participant's last radiographic time point.

Further details regarding the BIRC assessment will be provided in the BIRC charter.

The central review of the scans will be carried out in a blinded fashion. The decision regarding patient management will remain with the local investigator. Enrollment eligibility will be determined by the local staging assessment of the required images obtained during screening. Imaging studies used to determine eligibility must be submitted to the BIRC.

Disease characterization at baseline and evaluation of efficacy during study rely on the following:

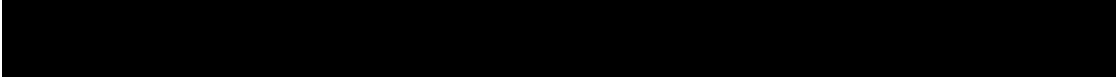
1. Pathology assessment
2. Imaging
3. Bone marrow biopsy or aspirate
4. CNS Brain Imaging (CT/MRI) and/or diagnostic lumbar puncture with CSF cytology (mandatory at screening and at discretion of the Investigator to evaluate CNS disease thereafter)
5. Lesions from physical exam findings
6. Procedures performed on study

Imaging data will be centrally collected and checked for quality by an imaging Contract Research Organization (CRO) designated by Novartis. The results of the central evaluations will be used for primary analysis purposes. The local investigator's assessment will be used for treatment decision making.

Any potentially measurable lesion that has been previously treated with radiotherapy should be considered as a non-measurable (non-index) lesion. However, if a lesion previously treated with radiotherapy has clearly progressed since the radiotherapy, it can be considered as a measurable lesion.

Imaging assessments

Imaging assessments will be performed at screening within D-14 to -1 of randomization. Screening/baseline imaging assessment should be done as close to randomization as possible.



In the event more than one imaging assessment is performed after ICF and prior to randomization then only the assessment date closest to randomization should be captured in the clinical database and used as the screening/baseline assessment.

Any imaging assessments, bone marrow biopsies, or lumbar punctures already completed during the regular care of the participant within 4 weeks prior to randomization, including before signing the main study ICF, can be considered as the screening disease assessments for this study. Any imaging or disease assessments obtained after randomization cannot be considered for screening. The patient should not receive any anticancer therapy between the screening disease assessments and randomization. One of the following assessments are required at screening, Week 6, Week 12, and Month 6 and at other timepoints only for new CR on CT scan not previously documented to confirm response:

1. PET-CT with diagnostic CT
2. PET-CT with non-diagnostic CT + dedicated diagnostic CT
3. Dedicated diagnostic CT + dedicated FDG PET

In Arm A, the Week 6 PET-CT is required to be done after the completion of all planned bridging chemotherapy and as close as possible before lymphodepleting chemotherapy.

In Arm B, the Week 6 PET-CT is required to be done no sooner than 14 days after the start of the second cycle of immunochemotherapy for R-DHAP, R-GDP, and R-ICE, or 7 days after the third cycle of immunochemotherapy for R-GemOx.

In patients that crossover to Arm A, the most recent imaging assessment prior to crossover will be considered the new baseline images to be used in the crossover evaluations. In most cases, this would be the imaging that was used to diagnose SD/PD. If this imaging was a CT scan only, the investigator should obtain a PET scan within 14 days of the CT scan, at or prior to the crossover visit to serve as new baseline images for the crossover evaluations.

In patients that crossover to Arm A, it is possible that the patient has tisagenlecleucel already available for infusion at the time of crossover due to an early manufacturing request. In this case the patient may proceed to infusion with no bridging and Week 6 would occur after infusion. If tisagenlecleucel is not available at the time of crossover, the Week 6 assessment should occur after the completion of bridging chemotherapy as in Arm A.

PET imaging is always required in order to confirm the first documented complete response (CR). If the first documented radiological CR is seen on CT scan only, a confirmatory PET scan (either FDG PET or PET-CT) should be obtained within 14 days in order to confirm that timepoint's response of CR. If the PET scan is not obtained within 14 days, the timepoint must be assessed as a PR, and the next scan should be done by one of the 3 methods above as soon as possible to confirm the CR. Once CR has been established by PET imaging, subsequent CR and/or PD may be followed by CT imaging only. The CT component of the PET-CT may be used in lieu of a standalone CT/MRI, only if the CT component is of similar diagnostic quality as a contrast enhanced CT performed without PET. If contrast enhanced PET-CT with diagnostic CT is not available, a standard FDG-PET must be performed and a standalone diagnostic CT/MRI should be performed in addition to the FDG-PET scan. If independent CT and PET scanners are used, and the participant is receiving both scans on the same day, the PET must be performed prior to the CT with IV contrast as to not compromise PET results. The PET-

CT acquisition methodology (e.g., administration of intravenous contrast) should remain consistent at all imaging visits for any given patient.

It is preferred to obtain a PET-CT with diagnostic CT at all protocol required imaging visits when possible.

If a participant is known to have a contraindication to CT intravenous (IV) contrast media or develops a contraindication during the trial, a non-contrast CT of the neck and chest (MRI is not recommended due to respiratory artifacts, however if CT is not feasible per local regulations, MRI can be performed instead) plus a contrast-enhanced MRI (if possible) of the abdomen and pelvis should be performed.

Brain MRI or CT or CSF evaluation is mandatory to be completed at screening and only completed post-randomization if clinically indicated. Contrast enhanced brain MRI is preferred, however, if MRI contrast is contraindicated, then MRI without contrast or CT with/without contrast is acceptable.

If skin lesions are identified as a result of a physical exam, these are to be documented via the Lugano classification 2014 assessment as a physical exam, skin lesion.

Additional imaging assessments may be performed at any time during the study at the investigator's discretion for suspicion of PD or to support the efficacy evaluations for a participant, as necessary. If imaging is done for safety reasons only there should be no efficacy assessment and/or submission to the imaging CRO. (All imaging submitted to the imaging CRO are expected to have a corresponding local efficacy assessment).

Any on protocol scheduled and/or unscheduled imaging assessments done within ± 14 day window are to be assessed under a single evaluation.

Clinical suspicion of disease progression at any time requires a physical examination and imaging assessments to be performed promptly rather than waiting for the next scheduled imaging assessment.



Table 8-5 Imaging or disease assessment collection plan

Procedure	Screening	Treatment Assessment
PET-CT with contrast enhanced diagnostic (Dx) CT - Neck, Chest, Abdomen, Pelvis	Mandated	Mandated at Week 6, Week 12, and at Month 6 May be used within 14 days at any visit a new CR by CT needs to be confirmed, not seen previously Once CR is confirmed with PET, additional PET imaging is not required (CT only)
Dedicated FDG PET	Mandated, if no Dx PET-CT available	Mandated at Week 6, Week 12, and Month 6, if no Dx PET-CT is available May be used within 14 days at any visit a new CR by CT needs to be confirmed, not seen previously Once CR is confirmed with PET, additional PET imaging is not required (CT only).
CT/MRI (Neck, Chest, Abdomen, Pelvis)	Mandated, if no Dx PET-CT available	Mandated at months 9, 12, 18, 24, 36, 48 and 60/EOT and any time to confirm PD or response. Mandated at Week 6, Week 12, and Month 6, if no Dx PET-CT available PET-CT with diagnostic CT is preferred at all imaging visits when possible.
Response (CR) confirmation by PET-CT or dedicated FDG PET	NA	PET imaging is required \pm 14 days within the same CT timepoint window when CR is seen by CT, only for new CR and not previously documented. Once CR has been confirmed PET imaging is no longer needed, however it is the preferred method when possible.
CT/MRI brain and/or CSF cytology	Mandated	As clinically indicated
Bone marrow aspirate and/or biopsy cells	Mandated	Mandated to confirm CR if bone marrow was involved by lymphoma prior infusion and as clinically indicated
Tumor biopsy (FFPE)	Mandated (used for pathology assessment and subtype determination; See Section 8.5.3)*	<ul style="list-style-type: none"> Recommended if PET shows residual metabolically active tissue to rule out interference of tisagenlecleucel activity with PET results. In addition, see Table 8-22 for mandatory exploratory collections. For patients enrolled in China, tumor biopsy will not be done as an exploratory assessment.
*For patients enrolled in China: Tumor biopsy must be done for eligibility and screening purposes with local pathology assessment; however the biopsies will not be submitted centrally.		

8.3.1 Transmission of efficacy data to BIRC

All radiological assessments will be read locally and should be submitted promptly after acquisition to the imaging vendor designated by Novartis. Rapid image transmission to the central imaging vendor will be accomplished by transferring the images acquired by the investigator electronically in a secured website (e.g.: via the internet). In all instances, the process at the imaging vendor will ensure that the central reviewers remain blinded to the treatment arm, the results of the local assessment, and the expedited nature of the review.

8.3.2 Non-expedited review - timepoints without locally determined progression or stable disease

All imaging time points without locally determined progression or stable disease per Lugano classification 2014 will be read on an ongoing non-expedited basis as detailed in the imaging

manual to be provided by the designated imaging vendor and independent review charter. Expedited review may be required if necessary. Results of these readings will not be communicated to the sites.

8.3.3 Expedited review - timepoints with locally determined progression or stable disease

All imaging time points in Arm A or Arm B (not including crossover) with locally determined progression or stable disease per Lugano classification 2014 will require an expedited review by the BIRC. The investigator must seek an expedited review and indicate this request to the imaging vendor on a designated form or by alternative means identified by the imaging vendor. The imaging CRO will ensure that the BIRC reviewers are blinded to the results of the local assessments and the nature of the expedited review.

Rapid image transmission to the imaging CRO may be accomplished by uploading all digital images acquired by the Investigator to the secure website provided by the imaging CRO (e.g., via the internet). The imaging will undergo expedited central review (within 5 business days from the time of the receipt of images at the imaging CRO and once all applicable image queries are resolved) and the results of the central review will be communicated to the site. While the investigator is awaiting the results of the BIRC from the imaging CRO confirming disease progression or stable disease, it is preferable that the patient continue on study treatment. However, during this time, the investigator should do whatever is medically necessary for his/her patient.

If the central review does not determine disease progression or stable disease per Lugano classification 2014, the patient should continue to have imaging performed as per protocol and receiving the study treatment until the central review determines progressive disease or stable disease unless there is a medical need (i.e., clinical deterioration) for an immediate change in therapy per the investigator's clinical judgment.

If the central review confirms disease progression or stable disease, treatment may be continued beyond Lugano classification 2014 defined SD/PD if, in the judgment of the investigator, there is evidence of clinical benefit and the patient wishes to continue on the study treatment.



In patients randomized to Arm B:

- If the central review confirms disease progression or stable disease at or after the week 6 ($\pm 2w$) assessment, then the physician may request a tisagenlecleucel manufacturing slot from the sponsor and change therapy as appropriate.
- If the central review confirms disease progression or stable disease at or after the week 12 ($\pm 1w$) assessment, then the patient may cross over from SOC treatment to tisagenlecleucel treatment strategy.
- Patients that proceed to transplant and do not experience SD/PD for 365 days after HSCT are no longer eligible for manufacturing request or crossover.

8.4 Safety

For details on AE collection and reporting, refer to [Section 10.1](#).

ECOG Performance status grade will be used as described in the [Table 8-6](#).

Table 8-6 **ECOG performance status grade**

Grade	ECOG
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

Physical assessments are specified below in [Table 8-7](#) , with the visit evaluation schedule detailing when each assessment is to be performed.

Table 8-7 Physical assessments

Assessment	Specification
Physical examination	<p>A complete evaluation will generally include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular and neurological (including ICANS & ICE if applicable). If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed.</p> <p>Significant findings that were present prior to the signing of informed consent must be included in the appropriate CRF page. Any lesions detected during a physical exam at any time-point that are not detectable by imaging should be recorded on the appropriate CRF page. Significant new findings, other than new lesions, that begins or worsens after informed consent must be recorded on the appropriate CRF page.</p>
Vital sign	<p>Vital signs include temperature, blood pressure, pulse rate, respiratory rate. Pulse oximetry is required as specified in the visit evaluation schedule.</p> <p>For patients receiving tisagenlecleucel, vital signs (temperature, respiration rate, pulse rate, pulse oximetry, and blood pressure) will be taken prior to, during and immediately after the infusion and then approximately every 15 minutes for one hour and then every hour for the next two hours, or until these signs are satisfactory and stable. Fever is frequently the first symptom of CRS and must be monitored following infusion.</p> <p>For all patients, systolic and diastolic blood pressure should be measured after the patient has been sitting for five minutes, with back supported and both feet placed on the floor, using an automated validated device, with an appropriately sized cuff. In case the cuff sizes available are not large or small enough for the patient's arm circumference, a sphygmomanometer with an appropriately sized cuff should be used.</p>
Height and weight	Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram [kg] in indoor clothing, but without shoes) will be measured.

8.4.1 Laboratory evaluations

Laboratory assessments are specified below in [Table 8-8](#) and [Table 8-9](#), with the visit evaluation schedule detailing when each assessment is to be performed.

Regular sample collections for serum cytokines, tisagenlecleucel cellular kinetics, and inflammatory markers (e.g. ferritin and CRP) are mandated during the first 28 days following tisagenlecleucel infusion. However, as the time-course and rapidity of CRS development varies among patients, additional unscheduled samples for these markers may also be collected as needed, if it is clinically feasible. Frequent monitoring of serum CRP, ferritin and cytokines should be considered during the clinical course of CRS of any severity (e.g. every day to several days) especially around the following clinical events: initial persistence of fevers, hemodynamic instability, initial and worsening of respiratory distress, rapid clinical deterioration, just prior to and daily for 2 days following tocilizumab administration, around other clinically significant events and upon the clinical resolution of CRS.

Please note that results of cytokine analyses are NOT to be used for clinical management decisions of CRS. A detailed treatment algorithm has been established with clear criteria for CRS management (see [Table 6-2](#) and [Table 6-3](#)).

Table 8-8 Laboratory assessments – Central Assessments

Test Category	Test Name
Hematology	Hematocrit, Hemoglobin, MCHC, MCV, Platelets, Red blood cells, White blood cells with complete differential (Basophils, Eosinophils, Lymphocytes, Atypical Lymphocytes, Monocytes, Neutrophils, Bands, Lymphoblasts, Plasma cells, Prolymphocytes, Myelocytes, Metamyelocytes, and Promyelocytes)
Chemistry	Glucose (fasting), Blood Urea Nitrogen (BUN), Creatinine, eGFR, Sodium, Potassium, Calcium, Magnesium, Phosphorous, Total Cholesterol, Triglycerides, Total Protein, Albumin, Total Bilirubin, Direct Bilirubin, Indirect Bilirubin, Amylase, Alkaline phosphatase, ALT (SGPT), AST (SGOT), Lipase, LDH, Ferritin, CRP, and Uric Acid
Cardiac Enzymes	Troponin I, NT-proBNP
Urinalysis	Macroscopic Panel (Dipstick) (Bilirubin, Blood, Glucose, Ketones, Leukocytes esterase, Nitrite, pH, Protein, Specific Gravity) If macroscopic panel is abnormal then perform microscopic panel (Red Blood Cells, White Blood Cells, Casts, Crystals, Bacteria, Epithelial cells)
Coagulation	Prothrombin time (PT) or International normalized ratio (INR), activated Partial thromboplastin time (aPTT), fibrinogen, and D-dimer
Viral Serology	Epstein-Barr Virus (EBV), Hepatitis C Virus (HCV) antibody, Hepatitis B surface antigen (HBsAg), Hepatitis B surface antibody (HBsAb), Hepatitis B core antibody (HBcAb), HIV test (if an initial HIV screening test is positive then a confirmatory HIV test is required to be performed as per current local guidelines). Additionally HBV DNA and HCV RNA testing may be conducted as per the algorithm in Section 16.1 Appendix 1 . Viral serology testing must be within 8 weeks prior to lymphodepletion and tisagenlecleucel infusion.
Additional tests	Serum immunoglobulin levels (IgG, IgA, IgM), RCL by VSV-g q-PCR
CD19	Immunohistochemistry or flow cytometry (Screening to randomization and as clinically indicated) For patients enrolled in China: Immunohistochemistry will not be done. Flow cytometry will be done only if approved by relevant Chinese Authorities.
NHL subtype determination	Immunohistochemistry (Screening to randomization) – Central assessment conducted for all randomized patients, but not used for eligibility For patients enrolled in China: This exploratory assessment is not to be done
c-myc, bcl-2 and bcl-6 expression	FISH (Screening to randomization) [as applicable] – Central assessment conducted for all randomized patients For patients enrolled in China: This exploratory assessment is not to be done.

Table 8-9 Laboratory Assessments – Local Assessments

Test Category	Test Name
Influenza	Rapid Influenza A & B Test
Pregnancy Test	Serum testing, Urine tests (kits are supplied by central vendor)
NHL subtype determination	Immunohistochemistry (Screening to randomization) – Local assessment is used for patient eligibility
c-myc, bcl-2 and bcl-6 expression	FISH (Screening to randomization) [as applicable] – Local assessment may be done at the time of NHL subtype determination
Additional Tests	Flow cytometry on leukapheresis product (needed to confirm acceptability of leukapheresis product as per Investigational Leukapheresis, Cryopreservation and Scheduling Manual)

8.4.2 Electrocardiogram (ECG)

ECGs must be recorded after 10 minutes rest in the supine position to ensure stable baseline. The preferred sequence of cardiovascular data collection during study visits is ECG collection first, followed by vital signs, and blood draws. The Fredericia QT correction formula (QTcF) should be used for clinical decisions.

Single 12-lead ECGs are to be collected. The original ECGs on a non-heat-sensitive paper or a certified copy on non-heat sensitive paper, appropriately signed, must be collected and archived at the study site.

For any ECGs with participant safety concerns, two additional ECGs must be performed to confirm the safety finding. A monitoring or review process should be in place for clinically significant ECG findings throughout the study and especially at baseline before administration of study treatment.

Any identifier details must be redacted, e.g. participant initials, date of birth.

In the event that a clinically significant ECG abnormality is identified at the site (e.g. severe arrhythmia, conduction abnormality of QTcF \geq 450 ms for males and QTcF \geq 460 ms for females), the ECG is to be repeated to confirm the diagnosis. If the participant is hemodynamically compromised, the investigator or a medically qualified person must initiate appropriate safety procedures without delay (for example cardioversion).

Clinically significant abnormalities must be recorded on the CRF as either medical history/current medical conditions or adverse events as appropriate

A standard 12-lead ECG will be performed

- at screening prior to randomization (any ECG already completed during the regular care of the participant within 4 weeks prior to randomization, including before signing the main study ICF, can be considered as the screening assessments for this study)
- on the day of but prior to tisagenlecleucel infusion for patients randomized to Arm A or crossover patients
- as clinically indicated and at crossover for patients randomized to Arm B

Interpretation of the tracing must be made by a qualified physician and documented on the appropriate CRF. Each ECG tracing should be labeled with the study number, participant initials (where regulations permit), participant number, date, and kept in the source documents at the study site. Clinically significant abnormalities present at screening should be reported on the appropriate CRF. Clinically significant findings must be discussed with Novartis prior to enrolling the participant in the study and reported on the appropriate CRF. New or worsened clinically significant findings occurring after informed consent must be recorded as adverse events.

Additional, unscheduled, safety ECGs may be repeated at the discretion of the investigator at any time during the study as clinically indicated. Unscheduled ECGs with clinically significant findings should be collected in triplicate. Local cardiologist ECG assessment may also be performed at any time during the study at the discretion of the investigator.

8.4.2.1 Cardiac imaging

An ECHO/MRA/MUGA test is required to be completed at screening and crossover. Any ECHO/MRA/MUGA test already completed during the regular care of the participant within 4 weeks prior to randomization, including before signing the main study ICF, can be considered as the screening assessments for this study. Clinically significant abnormalities present when the patient signed the informed consent should be reported on the appropriate eCRF page.



Clinically significant findings must be discussed with the Novartis Medical Monitor prior to enrolling the patient in the study. New or worsened clinically significant findings occurring after informed consent must be recorded on the Adverse Events CRF page. Patients must have a left ventricular ejection fraction (LVEF) $\geq 45\%$ to be included into the study.

8.4.2.2 Cardiac enzymes

Cardiac enzymes should be performed if clinically indicated as per the visit evaluation schedule.

8.4.3 Pregnancy and fertility

All WOCBP will have pregnancy testing. Additional pregnancy testing might be performed if requested by local requirements. For the frequency of pregnancy testing please refer to [Table 8-2](#), [Table 8-3](#), and [Table 8-4](#). For all pregnancy tests performed at home, the site personnel will follow-up with the participant via telephone call to collect the date and the test results and document the information in the participant's source documents.

For pregnancy reporting requirements and follow-up of the pregnancy outcome including the newborn refer to [Section 10.1.5](#).

The assessment of fertility done at screening should include discussion regarding the menstrual cycle and onset of the menopause, respectively.

For more information about the effects of tisagenlecleucel on reproduction please refer to the recent [Tisagenlecleucel Investigator's Brochure].

8.4.4 Spirometry

In order to assess, HSCT eligibility, a FEV1 or DLCO test should be performed at screening according to local institutional practice. Any spirometry test already completed during the regular care of the participant within 4 weeks prior to randomization, including before signing the main study ICF, can be considered as the screening assessments for this study.

8.4.5 Other safety evaluations

Humoral immunogenicity to tisagenlecleucel and detectable RCL will be assessed as described [Table 8-2](#) and [Table 8-4](#). If blood samples for RCL testing are negative through Month 12, all samples taken after Month 12 will be stored for potential future testing.

8.4.6 Appropriateness of safety measurements

The safety assessments selected are standard for this indication/participant population.

8.5 Additional assessments

8.5.1 Patient reported outcomes (PRO)

Three questionnaires will be used in this study to capture electronic patient reported outcomes (ePROs): the Short Form (36) Health Survey (SF-36 v2), the Functional Assessment of Cancer Therapy—Lymphoma (FACT-Lym version 4), and the EuroQol 5D (EQ-5D-5L) questionnaire.

Patient reported outcome data will be assessed during the study as indicated in [Table 8-1](#), [Table 8-2](#), [Table 8-3](#), and [Table 8-4](#). Descriptive statistics (e.g. mean, median and frequency) and change from baseline of the summary scores for each post baseline time-point/window of assessment will be provided by treatment arm. FAS will be used for all analysis.

Each of the questionnaires mentioned above is designed for patient self-administration. Method of activating and operating the data capture device is provided in a separate user guide.

The patient should be given the tablet to complete the questionnaire(s) at the scheduled visit prior to any testing, treatment, or discussion with the physician or clinical personnel. Patient refusal to complete all or any part of a PRO measure should be documented in the study data capture systems and should not be captured as a protocol deviation. The questions should be completed in the language the respondent is most familiar with, at the scheduled visit before the patient sees the investigator for clinical assessments. The patient should be given sufficient space and time to complete the PRO measures.

The responsible site personnel should check the patients' responses for completeness and encourage the patient to complete any missing responses. The responses stored electronically in the database will be considered the source file. Detailed instructions relating to the administrative procedures of the questionnaires will be provided to the sites.

The completed ePRO data and any unsolicited comments made by the patient should be reviewed and assessed by the investigator for responses which may indicate potential AEs, including SAEs, before any clinical study examinations. This assessment should be documented in study source records. If AEs or SAEs are confirmed, study investigators should not encourage the patient to change responses reported in the completed ePRO data.

Patients that crossover to the tisagenlecleucel arm will still need to complete the SF-36v2, FACT-Lym, and EQ-5D-5L at the same time points specified above and in [Table 8-4](#). The SF-36v2, FACT-Lym, and EQ-5D-5L should be collected at the EOT visit in patients that experience BIRC-confirmed PD/SD in Arm A (or patients that crossover from Arm B to Arm A), and in patients that experience BIRC-confirmed PD/SD in Arm B, but do not plan to crossover. Whenever possible, this collection should occur prior to initiation of new anticancer therapy. These patients should also complete the SF-36v2, FACT-Lym, and EQ-5D-5L at 4 weeks after PD/SD, 12 weeks after PD/SD, and 6 months after PD/SD.

Study investigators must follow reporting instructions outlined in [Section 10.1](#).

8.5.1.1 SF-36 v2 (acute form)

The 36-item short form (SF-36v2) is a generic quality of life measure used widely in clinical practice and research, general population surveys and health policy evaluations ([Ware and Sherbourne 1992](#)). The SF-36 v2 comprises 36 questions, which are summarized in eight health domain scores: Physical Functioning, Role-Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role-Emotional, and Mental Health. Two overall component summary scores, the Physical Component Summary (PCS) and the Mental Component Summary (MCS), also can be computed. Domain and component summary scores can be converted to norm-based scores. A higher SF-36 score denotes better HRQoL.

The SF-36 has proven useful in monitoring general and specific populations, comparing the relative burden of different disease, differentiating the health benefits produced by different treatments, and in screening individual patients. Although a generic HRQoL measure, the SF-36 is sensitive to variations in specific health states (known groups validity). For example, a study documenting the long term effects of NHL and its treatment found that those with comorbid health conditions had lower SF-36 physical functioning scores than those without such conditions ([Mols et al. 2007](#)).

8.5.1.2 FACT-Lym version 4

The Functional Assessment of Cancer Therapy-Lymphoma (FACT-Lym) is a questionnaire to assess the quality of life in patients with Lymphoma. The FACT-Lym questionnaire is composed of the FACT-General (FACT-G) – a 27-item compilation of general questions scored on a 5 point scale ranging from 0 = “not at all” to 4 = “very much” - and an additional 15 items that assess patient concerns relating to lymphoma: FACT-Lym lymphoma-specific subscale (FACT-LymS; range, 0-60).

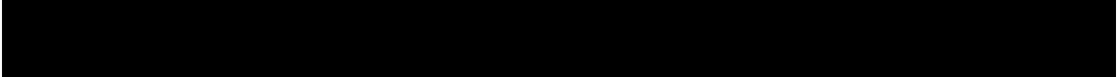
FACT-G items are divided into four primary HRQoL domains: PWB (Physical Well-Being; seven items, range 0-28), SWB (Social/Family Well-Being; seven items, range 0-28), EWB (Emotional Well-Being, six items, range 0-24), and FWB (Functional Well-Being and Additional Concerns; seven items range, 0-28).

The FACT-LymS consists of common lymphoma disease and/or treatment-related symptoms (e.g., pain, fever, swelling, night sweats, insomnia, itching, weight loss, fatigue, and loss of appetite). Two summary scales: FACT-Lym trial outcomes index (FACT-Lym TOI; range: 0-116; composed of the PWB, FWB, and FACT-Lym LYMS scales); FACT-Lym total score (FACT-Lym TS, range, 0-168; composed of all of the scales) can also be calculated. Negatively worded items are reverse scored prior to summing so that higher scores are reflective of better HRQoL.

This scale is designed for patient self-administration. Patients should be instructed to read the brief. After the patient's correct understanding has been confirmed they should be encouraged to complete every item in order without skipping any. Some patients may feel that a given question is not applicable to them and therefore will skip the item altogether. Patients should be encouraged to check the response most applicable.

8.5.1.3 EQ-5D-5L

The EQ-5D-5L is a widely used, self-administered questionnaire designed to assess health status in adults. The measure is divided into two distinct sections. The first section includes one item addressing each of five dimensions (mobility, self-care, usual activity, pain/discomfort, and anxiety/depression). Patients report each of these items from “no problem”, “slight problem”, “moderate problem”, “severe problem”, or “extreme problem.” A composite health index is then defined by combining the levels for each dimension. The second section of the questionnaire (EQ-VAS) measures self-rated (global) health status utilizing a vertically oriented visual analogue scale where 100 represents the “best possible health state” and 0 represents the “worst possible health state.” Respondents are asked to rate their current health by placing a



mark along this continuum. The recall period is “today,” and the questionnaire requires 5 to 10 minutes to complete.

8.5.1.4 Healthcare resource utilization regarding hospitalization

Hospitalizations will be evaluated in this study as an exploratory endpoint to characterize the impact of study treatment on this aspect of healthcare resource utilization. These data may be used to support assessments used to characterize the economic impact of study treatment regimens.

Hospitalization data of interest will focus on those hospitalizations reported within the first 6 months after treatment. Hospitalizations as a result of the following reasons are not to be reported:

- Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
- Social reasons and respite care in the absence of any deterioration in the patient’s general condition
- Treatments occurring on an emergency outpatient basis that does not result in hospital admission and involves an event not fulfilling any of the definitions of a SAE as described in [Section 10.1.2](#).

Healthcare resource utilization data regarding hospitalizations should be captured from randomization (Day 1) up to Month 6 for the patient as described in [Table 8-1](#), [Table 8-2](#), [Table 8-3](#), and [Table 8-4](#).

Information related to the length of stay (e.g., dates of admission or discharge), hospital ward facilities used (e.g., emergency department, intensive care unit, general ward, etc.), reasons for hospitalization as associated with the study treatment regimen, disease and/or disease progression, or any other reason will be of interest; and hospital discharge information will be evaluated.

8.5.2 Pharmacokinetics/ Cellular Kinetics

Cellular kinetic samples will be collected in all participants at the visits defined in the assessment schedule. Follow instructions outlined in the [\[CCTL019H2301 Laboratory Manual\]](#) regarding sample collection, numbering, processing and shipment. See the potential use of residual samples for more information.

In order to better define the kinetic profile, the timing of the kinetic sample collection may be altered based on emergent data.

The number of samples/blood draws and total blood volume collected will not exceed those stated in the protocol.

Tisagenlecleucel transgene and surface expression measurement

Tisagenlecleucel concentrations in peripheral blood (and bone marrow, CSF, and other tissues if available) will be listed, graphed and summarized by time points as assessed by the following:

- Tisagenlecleucel transgene levels as measured by q-PCR



- Tisagenlecleucel transduced cells measured by flow cytometry of CD3-positive/ CD4-positive and CD3-positive/CD8-positive tisagenlecleucel transduced cells if feasible.*

*For patients enrolled in China: Flow cytometry measurements of cellular kinetics are considered an exploratory endpoint for this study. This assessment is only to be done if approval has been obtained by all relevant Chinese authorities.

The cellular kinetics parameters, based on transgene levels measured using qPCR, listed in Table 8-10 along with other relevant cellular kinetics parameters will be estimated, if feasible, from the individual concentration versus time profiles using a non-compartmental approach within the modeling program Phoenix WinNonlin[®] Version 6.4 (Pharsight, Mountain View, CA) and reported by response category. The non-quantifiable concentrations will be imputed to zero for concentration summaries, and will not be included for estimation of cellular kinetics parameters. Results reported but deemed unreliable will be flagged and excluded from the summaries and cellular kinetics parameter derivations.

Descriptive statistics of cellular kinetics parameters (arithmetic and geometric means, standard deviation, CV%, CV% geometric mean, minimum, median and maximum) will be summarized by best overall response for all patients who receive tisagenlecleucel in arm A or after crossover. For T_{max} only minimum, median and maximum will be presented.

The linear trapezoidal linear interpolation rule will be used for AUC calculation. Regression analysis of the terminal plasma elimination phase for the determination of $T_{1/2}$ will include at least 3 data points after C_{max} . If the adjusted R^2 value of the regression analysis of the terminal phase will be less than 0.6, no values will be reported for $T_{1/2}$.

Table 8-10 Non compartmental cellular kinetics parameters

Parameter	Definition
AUC 0 - 28d and/or AUC0-84d	The AUC from time zero to day 28 and/or day 84 and or other disease assessment days, in peripheral blood (days*copies/ μ g)
C_{max}	The maximum (peak) observed in peripheral blood or other body fluid drug concentration after single dose administration (copies/ μ g)
T_{max}	The time to reach maximum (peak) peripheral blood or other body fluid drug concentration after single dose administration (days)
$T_{1/2}$	The half-life associated with the elimination phase slope of a semi logarithmic concentration-time curve (days) in peripheral blood
C_{last}	The last observed quantifiable concentration in peripheral blood (copies/ug)
T_{last}	The time of last observed quantifiable concentration in peripheral blood (days)

Summary of cellular kinetics by CRS grade and use of tocilizumab

For patients who receive tocilizumab for management of CRS, the cellular kinetic parameters will be summarized by use of tocilizumab and CRS grades.

Table 8-11 Validated analytical methods and limit of quantification associated with the cellular kinetic analytes and immunogenicity assessments

Analyte	Analytical method	Units	Lower limit of quantification (LLOQ)	Type of biological sample	Dataset
tisagenlecleucel transgene	Quantitative polymerase chain reaction (qPCR)	copies/µg and/or copies/ µL	10 copies/reaction equivalent to approx. 50 copies/ug of genomic DNA	Peripheral blood	PAS
Surface expression of CAR positive cells	Flow cytometry	% of CD3+ T cells	0.5% of CD3+ T cells	Peripheral blood	PAS
Anti-mCAR antibodies (Humoral immunogenicity)	Flow cytometry	MFI (mean fluorescence intensity)	NA Response compared to respective CP defined during validation	Serum	Safety set
Antigen specific T cell lymphocytes (Cellular immunogenicity)	Intracellular Interferon gamma staining and flow cytometry	% IFNgamma+ CD4/CD8 T cells (for both pool 1 and pool 2)	IFNgamma+ CD4 T cells: LLOQ for SEB treated PBMC is 0.083% IFNgamma+ CD8 T cells: LLOQ for SEB treated PBMC is 0.062% LLOQ for CEF treated PBMC is 0.059%	PBMC	Safety set

8.5.2.1 Cellular kinetic blood collection and handling

Sample(s) will be collected at the time point(s) defined in the assessment schedules below.

Refer to the [\[CCTL019H2301 Laboratory Manual\]](#) for detailed instructions for the collection, numbering, processing, handling, and shipment of kinetic samples.



Table 8-12 Tisagenlecleucel cellular kinetics by qPCR in peripheral blood collection log for patients in screening to randomization, Arm A, and in patients that cross over from Arm B to Arm A.

Cycle	Day**	Scheduled Time Point relative to dosing*	Screening to Randomization		Arm A		Cross over from Arm B to Arm A		
			Dose Reference ID	PK1 Sample No	Dose Reference ID	PK1 Sample No	Dose Reference ID***	PK1 Sample No	Sample Volume (ml)
1	D1 Randomization	Pre-dose	-	101	-	-	-	-	3
1	Unscheduled cellular kinetic samples ^a	Pre-dose	-	10101	-	-	-	-	3
1	Infusion (immediately prior to infusion)	D1 (Pre-dose)	-	-	1	102	-	-	3
1	Infusion +1d	D2	-	-	1	103	-	-	3
1	Infusion +3d ±1d	D4	-	-	1	104	2	201	3
1	Infusion +6d ±1d	D7	-	-	1	105	2	202	3
1	Infusion +10d ±3d	D11	-	-	1	106	2	203	3
1	Infusion +13d ±3d	D14	-	-	1	107	2	204	3
1	Infusion + 21d ±3d	D22	-	-	1	108	2	205	3
1	Infusion + 28d ±7d	D29	-	-	1	109	2	206	3
1	Week 12 ±7d	Week 12 – RTI*	-	-	1	110	2	207	3
1	M4±14d	M4 – RTI*	-	-	1	111	2	208	3
1	M6±14d	M6 – RTI*	-	-	1	112	2	209	3
1	M9±14d	M9 – RTI*	-	-	1	113	2	210	3
1	M12±14d	M12 – RTI*	-	-	1	114	2	211	3
1	M18±14d	M18 – RTI*	-	-	1	115	2	212	3
1	M24±14d	M24 – RTI*	-	-	1	116	2	213	3
1	M36±14d	M36 –RTI*	-	-	1	117	2	214	3
1	M48±14d	M48 – RTI*	-	-	1	118	2	215	3
1	M60±14d	M60 – RTI*	-	-	1	119	2	216	3

Cycle	Day**	Scheduled Time Point relative to dosing*	Screening to Randomization		Arm A		Cross over from Arm B to Arm A		
			Dose Reference ID	PK1 Sample No	Dose Reference ID	PK1 Sample No	Dose Reference ID***	PK1 Sample No	Sample Volume (ml)
1	Unscheduled cellular kinetic samples related to CRS ^b		-	-	1	10131	2	10201	3
1	Unscheduled (cellular kinetic samples related to non-CRS safety events) ^c		-	-	1	10151	2	10251	3
1	Unscheduled (cellular kinetic samples at relapse) ^d		-	-	1	10175	2	10275	3

*RTI refers to the time period between randomization (or the crossover visit) to infusion. Since the time between randomization (or crossover visit) and infusion will be variable between patients, samples collected from Week 12 onward will have a variable time from the date of infusion, represented by the difference between the visit time and the RTI time.

**Additional unscheduled samples may be collected as needed dependent upon individual patient differences in the clinical time-course of CRS, if clinically feasible.

***The DRID of 2 refers to the first dose received for patients in the crossover arm and patients will not receive more than one dose of tisagenlecleucel, this distinguishes the dose reference ID from patients originally randomized to Arm A.

a. Unscheduled cellular kinetic samples for Screening to Randomization arm are uniquely, sequentially numbered as 10101, 10102 etc,

b. Unscheduled cellular kinetic samples related to a CRS events whereby tocilizumab is not administered are uniquely, sequentially numbered as 10131, 10132 etc. for Arm A; and 10201, 10202 etc, for Crossover Arm. See [Table 8-18](#) for tisagenlecleucel kinetic collections (qPCR) when tocilizumab is administered during CRS.

c. Unscheduled anytime cellular kinetic qPCR samples related to other non-CRS safety events will be uniquely, sequentially numbered 10151, 10152 etc. for Arm A and 10251, 10252 etc for Crossover Arm. Samples collected in this category also include additional qPCR samples collected to monitor the need for contraception during the long-term additional follow-up (after BIRC-confirmed SD/PD).

d. In the event patient relapses, an unscheduled cellular kinetic sample should be collected along with corresponding immunogenicity sample (refer to [Table 8-16](#) and [Table 8-17](#)), and will be uniquely, sequentially numbered 10175, 10176 etc for Arm A and 10275, 10276 for Cross-over Arm.

Table 8-13 Tisagenlecleucel cellular kinetics by flow cytometry in peripheral blood collection log for patients in screening to randomization, and Arm A, and in patients that cross over from Arm B to Arm A.

Cycle	Day**	Screening to Randomization			Arm A		Crossover from Arm B to Arm A		
		Scheduled Time Point relative to dosing*	Dose Reference ID	PK2 Sample No	Dose Reference ID	PK2 Sample No	Dose Reference ID***	PK2 Sample No	Sample Volume (ml)
1	Infusion +10d ±3d	D11	-	-	1	301	2	401	2
1	Infusion + 28d ±7d	D29	-	-	1	302	2	402	2
1	Week 12 ±7d	Week 12 – RTI*	-	-	1	303	2	403	2
1	Unscheduled cellular kinetic samples related to CRS ^a		-	-	1	10831	2	10401	2
1	Unscheduled (cellular kinetic samples related to non-CRS safety events) ^b		-	-	1	10851	2	10451	2
1	Unscheduled (cellular kinetic samples at relapse) ^c		-	-	1	10875	2	10476	2

* RTI refers to the time period between randomization (or the crossover visit) to infusion. Since the time between randomization (or the crossover visit) and infusion will be variable between patients, samples collected from Week 12 onward will have a variable time from the date of infusion, represented by the difference between the visit time and the RTI time.

**Additional unscheduled samples may be collected as needed dependent upon individual patient differences in the clinical time-course of CRS, if clinically feasible.

***The DRID of 2 refers to the first dose received for patients in the crossover arm and patients will not receive more than one dose of tisagenlecleucel, this distinguishes the dose reference ID from patients originally randomized to Arm A.

^a. Unscheduled cellular kinetic samples related to a CRS events whereby tocilizumab is not administered are uniquely, sequentially numbered 10831, 10832 etc. for Arm A and 10401, 10402 etc. for Crossover arm. See [Table 8-18](#) for tisagenlecleucel PK collections (qPCR) when tocilizumab is administered during CRS.

^b. Unscheduled anytime cellular kinetic samples related to other non-CRS safety events will be uniquely, sequentially numbered 10851, 10852 etc. for Arm A and 10451, 10452 etc. for Crossover Arm.

^c. In the event patient relapses, an unscheduled cellular kinetic sample should be collected along with corresponding immunogenicity sample (refer to [Table 8-16](#) and [Table 8-17](#)) and are uniquely and sequentially numbered as 10875, 10876, etc., and 10476, 10477, etc for the Crossover Arm.

Note for patients enrolled in China: Flow cytometry samples are only to be collected if approval is obtained by all relevant Chinese authorities.

Table 8-14 **Tisagenlecleucel cellular kinetics by q-PCR in bone marrow aspirate collection log for patients in screening to randomization, Arm A, and for patients that cross over from Arm B to Arm A.**

			Screening to Randomization		Arm A		Crossover from Arm B to Arm A		
Cycle	Day	Scheduled time point relative to dosing*	PK DRID (CTL019)	PK3 Sample No. (CTL019)	PK DRID (CTL019)	PK3 Sample No. (CTL019)**	PK DRID (CTL019)***	PK3 Sample No. (CTL019)**	Sample Volume (mL)
1	Week 12±7d	Week 12 – RTI*	-	-	1	501	2	601	3
1	Unscheduled (e.g. at time of radiological CR, related to relapse) ¹		-	-	1	10551	2	10601	3

* RTI refers to the time period between randomization (or the crossover visit) to infusion. Since the time between randomization (or the crossover visit) and infusion will be variable between patients, samples collected from Week 12 onward will have a variable time from the date of infusion, represented by the difference between the visit time and the RTI time.

** Bone Marrow to be collected at or after Week 12 only if prior history of BM involvement, as clinically indicated in case of radiological CR.

***The DRID of 2 refers to the first dose received for patients in the crossover arm and patients will not receive more than one dose of tisagenlecleucel, this distinguishes the dose reference ID from patients originally randomized to Arm A.

¹ Unscheduled cellular kinetic samples will be uniquely, sequentially numbered 10551, 10552 etc. for patient in Arm A and 10601, 10602 etc. for patient in Crossover Arm

Table 8-15 **Tisagenlecleucel cellular kinetics by q-PCR in CSF**

To be completed only if CSF collection performed.

	Arm A	Crossover from Arm B to Arm A	
Day/ Scheduled Time Point	PK5 Sample No. (CTL019)	PK5 Sample No. (CTL019)	Sample Volume
Unscheduled (e.g. related to adverse event/relapse) ¹	10801	10901	4-8 mL

¹Unscheduled cellular kinetic samples for Arm A will be uniquely, sequentially numbered 10801, 10802 etc., while for crossover arm, the samples will be numbered 10901, 10902 etc., respectively.

Table 8-16 Humoral Immunogenicity serum sample collection for patients in screening to randomization, and Arm A, and in patients that cross over from Arm B to Arm A.

		Screening to Randomization	Arm A	Cross over from Arm B to Arm A	Sample volume (mL)
Day/ Scheduled Time Point	Scheduled time point relative to dosing*	IG1 Immunogenicity Sample Number	IG1 Immunogenicity Sample Number	IG1 Immunogenicity Sample Number	
D1 Randomization	Pre-dose	1101	-	-	3
Unscheduled samples ¹	Pre-dose	11151	-	-	3
Infusion -1d (pre-infusion)	D-1 (Pre-dose)	-	2101	3101	3
Infusion +13d ±3d	D14	-	2102	3102	3
Infusion +28d ±7d	D29	-	2103	3103	3
M4±14d	M4- RTI*	-	2104	3104	3
M6±14d	M6- RTI*	-	2105	3105	3
M12±14d	M12- RTI*	-	2106	3106	3
M18±14d	M18- RTI*	-	2107	3107	3
M24±14d	M24- RTI*	-	2108	3108	3
M60 ±14d /EOT	M60- RTI*	-	2109	3109	3
Unscheduled (at relapse)**.2		-	12151	13151	3
Unscheduled (e.g. related to safety events) ³		-	12175	13175	3

* RTI refers to the time period between randomization (or the crossover visit) to infusion. Since the time between randomization (or the crossover visit) and infusion will be variable between patients, samples collected from Week 12 onward will have a variable time from the date of infusion, represented by the difference between the visit time and the RTI time

** In the event patient relapses, an unscheduled humoral immunogenicity sample should be collected along with corresponding cellular kinetic sample (refer to [Table 8-12](#), [Table 8-13](#), [Table 8-14](#), and [Table 8-15](#))

¹Unscheduled humoral immunogenicity samples are uniquely, sequentially numbered 11151, 11152 etc. for Screening to Randomization Arm.

²Unscheduled humoral immunogenicity samples related to a relapse are uniquely, sequentially numbered 12151, 12152 etc. for Arm A and 13151, 13152 etc. for Crossover arm.

³Unscheduled humoral immunogenicity samples related to safety events will be uniquely, sequentially numbered 12175, 12176 etc. for Arm A and 13175, 13176 etc. for Crossover Arm.

Note: Long-term additional follow-up collection after SD/PD confirmed by BIRC as per [Table 8-2](#) and [Table 8-4](#) are collected with the same sample numbers as at Month 6 and 12 above. Month 9 can be collected as unscheduled visit.

Table 8-17 Cellular Immunogenicity peripheral blood sample collection log for patients in screening to randomization, and Arm A, and in patients that cross over from Arm B to Arm A.

	Scheduled time point relative to dosing*	Screening to Randomization	Arm A	Cross over from Arm B to Arm A	Sample volume (mL)
Day/ Scheduled Time Point		IG2 Immunogenicity Sample Number	IG2 Immunogenicity Sample Number	IG2 Immunogenicity Sample Number	
D1 Randomization	Pre-dose	4101	-	-	6
Unscheduled samples ¹	Pre-dose	14151	-	-	6
Infusion-1d (pre-infusion)	D-1 Pre-dose	-	5101	6101	6
Infusion + 13d ±3d	D14	-	5102	6102	6
Infusion + 28d ±7d	D29	-	5103	6103	6
M4±14d	M4- RTI*	-	5104	6104	6
M6±14d	M6- RTI*	-	5105	6105	6
M12±14d	M12- RTI*	-	5106	6106	6
M18±14d	M18- RTI*	-	5107	6107	6
M24±14d	M24- RTI*	-	5108	6108	6
M60 ±14d /EOT	M60- RTI*	-	5109	6109	6
Unscheduled (at relapse)**.2		-	15151	16151	6
Unscheduled (e.g. related to safety events) ³		-	15175	16175	6

* RTI refers to the time period between randomization (or the crossover visit) to infusion. Since the time between randomization (or the crossover visit) and infusion will be variable between patients, samples collected from Week 12 onward will have a variable time from the date of infusion, represented by the difference between the visit time and the RTI time

** In the event patient relapses, an unscheduled cellular immunogenicity sample should be collected along with corresponding cellular kinetic sample (refer to [Table 8-12](#), [Table 8-13](#), [Table 8-14](#), and [Table 8-15](#))

¹Unscheduled cellular immunogenicity samples are uniquely, sequentially numbered 14151, 14152 etc. for Screening to Randomization Arm.

²Unscheduled cellular immunogenicity samples related to a relapse are uniquely, sequentially numbered 15151,15152 etc.for Arm A and 16151, 16152 etc. for Crossover arm.

³Unscheduled cellular immunogenicity samples related to safety events will be uniquely, sequentially numbered 15175, 15176 etc. for Arm A and 16175, 16176 etc. for Crossover Arm.

Note: Long-term additional follow-up collection after SD/PD confirmed by BIRC as per [Table 8-2](#) and [Table 8-4](#) are collected with the same sample numbers as at Month 6 and 12 above. . Month 9 can be collected as unscheduled visit.

Table 8-18 Tisagenlecleucel cellular kinetics by qPCR in tocilizumab treated patients during CRS in Arm A and in patients that crossover from Arm B to Arm A

Day/ Scheduled Time Point**/**	Toci Dose Reference ID	tisagenlecleucel Dose Reference ID [§]	tisagenlecleucel cellular kinetics by qPCR Sample Number [^]	Sample Volume (whole blood)
D1 1h ± 15 min post infusion	101	1/2	251	2 mL
D2 ± 2h	101	1/2	252	2 mL
D3 ± 4h	101	1/2	253	2 mL
D7 ± 1d	101	1/2	254	2 mL
D1 (pre-dose; second infusion)	101	1/2	255	2 mL
D2 ± 2h from second infusion	102	1/2	256	2 mL
D3 ± 4 hours (post second infusion)	102	1/2	257	2 mL
D7±1d (post second infusion)	102	1/2	258	2 mL
D1 (5-15 minutes pre-dose; additional infusion)	102	1/2	259	2 mL
D2 ± 2 hours	103	1/2	260	2 mL
D3 ± 4 hours	103	1/2	261	2 mL
D7 ± 1d	103	1/2	262	2 mL
Unscheduled***	104,105	1/2	10263, 10264, 10265, 10266	2 mL

* Scheduled timepoints are relative to date of tocilizumab infusion

**Samples may be collected as needed dependent upon administration of tocilizumab, if clinically feasible.

§ For patients in Arm A, the tisagenlecleucel dose reference ID will be 1, while for patients in Crossover Arm, the tisagenlecleucel dose reference ID will be 2. Patients in either arm will not receive more than one dose of tisagenlecleucel.

Unscheduled tisagenlecleucel cellular kinetics sample collections related to CRS as specified in Table 8-12 will cease once cellular kinetic sample collections related to tocilizumab administration commence according to Table 8-18, if applicable.

[^] Cellular kinetic collections for CTL019 measured by qPCR will be numbered starting with 251, 252 etc. series

*** Unscheduled cellular kinetic samples collected in the event more than 2 tocilizumab doses are administered should follow additional cellular kinetic collection and numbering schedule (eg. 10263, 10264, etc).



8.5.2.2 Analytical method

All the cellular kinetic analytes along with the analytical methods and the associated limit of quantification are summarized in [Table 8-11](#).

8.5.3 Biomarkers

Sample(s) will be collected at the time point(s) defined in the assessment schedule.

In patients enrolled in China, samples for B cell levels, T cell levels and serum cytokine analysis should be collected, only if approved by all relevant Chinese authorities. Samples for central tumor biopsy analysis and peripheral blood immunophenotyping, gene expression profiling, and ctDNA plasma for MRD and tumor clonal analysis by Ig deep sequencing are not to be collected in patients enrolled in China.

Follow instructions for sample collection, numbering, processing and shipment provided in the [\[CCTL019H2301 Laboratory Manual\]](#).

Biomarker analyses will focus on:

1. Analysis of the molecular characteristics of baseline, relapsed and progression biopsies and how they correlate with and/or predict clinical response
2. Correlation analysis of biomarker measurements performed pre- and post-infusion with key outcomes of efficacy and safety such as CRS
3. The identification of biomarkers predictive of response to tisagenlecleucel treatment from apheresis product and tisagenlecleucel product in order to support patient selection and guide combination treatments

Analysis of tumor biopsy:

A recent tumor sample obtained after relapse/progression to front line therapy for the purpose of the study must be collected, if not already available. If a biopsy after relapse progression is not available, and it is not clinically feasible to obtain a new biopsy, an archival tumor biopsy from the initial diagnosis may be utilized. For patients who are PR after 6 cycles of first line therapy, archival tumor biopsy is not allowed. Clinical eligibility is based on local histology assessment; however, every effort should be made to submit the tumor biopsy to the central laboratory (For patients enrolled in China, tumor biopsy will not be submitted centrally). Excisional biopsies should be submitted wherever possible; in cases where this is not possible, a core needle biopsy is allowable. Fine needle aspiration (FNA) is not preferred. The tumor biopsy should only be submitted and will only be analyzed for patients that are randomized (not screen failures) (For patients enrolled in China, tumor biopsy will not be submitted centrally). In addition, the local pathology report with medical history (e.g. history of prior lymphoma transformation) should be sent along with the tumor biopsy.

DLBCL sub-typing will be performed by a central laboratory (For patients enrolled in China, tumor biopsy will not be submitted centrally).

Characterization of key biomarkers such as CD19, PD-1 and/or PD-L1, IDO1 on baseline, on treatment and relapsed tumor biopsies will be performed using assays such as immunohistochemistry, immuno-fluorescence, DNA and RNA analysis) as indicated in [Table](#)

8-2, Table 8-4, and Table 8-22 (These samples will not be collected for patients enrolled in China). In addition, information about CD19 positivity status based on local histology assessment will be collected when available.

Tumor samples collected in the course of the study may be used for additional exploratory biomarker analysis aimed at identification of potential biomarkers that could be prognostic or predictive of antitumor activity (or lack thereof) to study treatment (These samples will not be collected for patients enrolled in China).

Additional assessments that could be conducted include (These samples will not be collected for patients enrolled in China):

1. Presence/absence and/or localization of immune cells subsets (e.g. T cells, Treg cells, macrophages) in all patients or in specific subset of patients.
2. Expression and/or localization of additional immunohistochemical markers.
3. Tumor samples may be also used for gene expression profiling (e.g. nanostring, RNAseq) to correlate immune signatures or other expression markers with response to treatment.
4. Sequencing of specific genes, or whole exome sequencing. This analysis will explore the presence of oncogenic drivers and their impact on antitumor activity of the study treatment. The sequencing data may also be used to explore the mutational load and neoantigenic potential of the tumor cells

Soluble immune markers:

The serum levels of inflammatory cytokines and other soluble factors will be assessed pre- and post- tisagenlecleucel administration. These data will be used in order to attempt to retrospectively identify candidate serum markers potentially correlated with tisagenlecleucel efficacy, CRS severity and possible CNS toxicity. In patients enrolled in China, these markers should be done, only if approved by all relevant Chinese authorities.

Peripheral blood:

The effect of tisagenlecleucel therapy on B and T cell levels will be measured in peripheral blood to assess on-target effect on these CD19 positive cells. In patients enrolled in China, these should be done, only if approved by all relevant Chinese authorities.

Peripheral blood leukocytes characterization will include immunophenotyping and T cell subset analysis, and may also include transcriptome analysis and single nucleotide polymorphism (SNP) analysis. Comprehensive DNA sequencing is within scope of these analyses (in accordance with local regulations); at a minimum, targeted sequencing of genes relevant to the tisagenlecleucel mechanism of action will be conducted. In patients enrolled in China, these will not be done.

Analysis of peripheral blood leukocyte characteristics will be performed to identify potential markers associated with tisagenlecleucel efficacy, expansion and safety. The correlation between characteristics of tisagenlecleucel cell product and apheresis product with cellular kinetic parameters, clinical efficacy and safety endpoints will also be explored. In patients enrolled in China, these will not be done.

Composition of T cell subsets and cell lineages in peripheral blood and apheresis product with progressive disease may also be assessed. In patients enrolled in China, these will not be done

Minimal Residual Disease and tumor evolution:

Immunoglobulin (Ig) deep sequencing may be performed on bone marrow, whole blood, tumor or circulating tumor DNA when available, to identify prognostic and predictive value of minimal residual disease (MRD) and tumor clonality evolution. These analyses will be conducted on baseline samples, on-study samples, and samples collected at relapse and progression (This test will not be done for patients enrolled in China).



Table 8-19 Biomarker sample collection- peripheral blood for serum cytokine and soluble marker analyses

Day/ Scheduled Time Point*	Patients receiving the tisagenlecleucel (Arm A, or crossover patients)	Arm B
D1 Randomization	5 mL	5 mL
Infusion -7d to Infusion -3d; Lymphodepletion Chemotherapy	5 mL	
Infusion -1d; Pre-tisagenlecleucel infusion	5 mL	
Infusion +1d	5 mL	
Infusion +3d ±1d	5 mL	
Infusion +6d ±1d	5 mL	
Infusion + 10d ±3d	5 mL	
Infusion + 13d ±3d	5 mL	
Infusion + 21d ±3d	5 mL	
Infusion +28d ±7d	5 mL	
Week 12±7d	5 mL	
M6±14d	5 mL	
M12±14d	5 mL	
Unscheduled (samples related to CRS, samples related to relapse or safety events),	5 mL	
* All measurement times are relative to date of randomization unless otherwise specified. For patients enrolled in China: This sample should be collected only if approval has been obtained by all relevant Chinese authorities.		

Table 8-20 Biomarker sample collection – B cell levels (peripheral blood)

Day/ Scheduled Time Point*	Patients receiving the tisagenlecleucel (Arm A, or crossover patients)	Arm B
Day -14 ±7d to Day -1 Screening (prior to leukapheresis)	5 mL (Arm A only)	5 mL
D1 Randomization	5 mL	5 mL
Infusion -7d to Infusion -3d; LD	5 mL	
Infusion -1d Pre-tisagenlecleucel infusion	5 mL	
Infusion + 6d ±1d	5 mL	
Infusion + 10d ±3d	5 mL	
Infusion + 13d ±3d	5 mL	
Week 12±7d	5 mL	5 mL
M6±14d	5 mL	5 mL
M12±14d	5 mL	5 mL
M18±14d	5 mL	5 mL
M24±14d	5 mL	5 mL
M36±14d	5 mL	5 mL
M48±14d	5 mL	5 mL
M60 ±14d End of Treatment and Follow-up	5 mL	5 mL
Unscheduled (e.g. related to relapse)	5 mL	5 mL
Long Term Additional Follow-up (as per visit evaluation schedule)	5 mL	
<p>* All measurement times are relative to date of randomization unless otherwise specified. For patients enrolled in China: This sample should be collected only if approval has been obtained by all relevant Chinese authorities.</p>		

Table 8-21 Biomarker sample collection – immunophenotyping, gene expression profiling, (peripheral blood) and ctDNA plasma for MRD and tumor clonal analysis by Ig deep sequencing

Day/ Scheduled Time Point*	Patients receiving the tisagenlecleucel (Arm A, or crossover patients)**	Arm B
D1 Randomization	12.5 mL	12.5 mL
Infusion -7d to Infusion -3d; Lymphodepletion Chemotherapy	12.5 mL	
Infusion -1d; Pre-tisagenlecleucel infusion	12.5 mL	
Infusion +6d ±1d	12.5 mL	
Infusion +10d ±3d	12.5 mL	
Infusion +28d ±7d	12.5 mL	
Week 12±7d	12.5 mL	
M6±14d	12.5 mL	
M9±14d	12.5 mL	
M12±14d	12.5 mL	
M18±14d	12.5 mL	
M24±14d	12.5 mL	
M36±14d	12.5 mL	
M48±14d	12.5 mL	
M60±14d End of Treatment and Follow-up	12.5 mL	
Unscheduled (e.g. related to relapse)	12.5 mL	
Peripheral blood before leukapheresis		
D-14 ±7d to D-1 Screening	6 mL	
Leukapheresis product		
D-14 ±7d to D-1 Screening	2 mL	
<p>* All measurement times are relative to date of randomization unless otherwise specified.</p> <p>** The 12.5 mL collected includes 10 mL for immunophenotyping and 2.5 mL for gene expression profiling</p> <p>For patients enrolled in China: This sample will not be collected.</p>		

Table 8-22 Sample collection – biomarker exploratory analysis and CAR expression on tumor biopsy

Mandatory, if accessible and does not impact treatment

Day/Scheduled Time Point*	Sample Number	Arm A or crossover patients	Arm B
D-14 ±7d to D-1 Screening**	11301	X	X
Infusion +2d to Infusion +10d***	11302	X	
Week 12	11303	X	
****Unscheduled at relapse or progression in patients following tisagenlecleucel infusion (or as clinically indicated), and if available post-mortem from autopsy material following relapse or progression	11351	X	
<p>*All measurement times are relative to date of randomization unless otherwise specified. **A FFPE tumor biopsy is needed at screening for diagnosis confirmation ***This timepoint collection is optional and not mandatory ****Unscheduled collection related to relapse or progression: a FFPE tumor biopsy (excisional or core needle) is mandatory if accessible and does not impact treatment. A FFPE tumor biopsy (excisional or core needle) as clinically indicated should be submitted if PET-CT shows residual metabolically active tumor tissue. CAR expression will be measured to assess cellular kinetics in tumor biopsy samples, if available For patients enrolled in China: This sample will not be collected.</p>			

8.5.3.1 Optional additional biomarker studies using remaining samples

If the patient agrees, the remaining biomarker, and/or cellular kinetic samples as well as any remaining tisagenlecleucel product may be stored for up to 15 years and further analyzed to address scientific questions related to tisagenlecleucel or cancer or for studies related to improvements in the manufacturing process. A decision to perform such additional research studies would be based on outcome data from this study or from new scientific findings related to the drug class or disease, as well as reagent and assay availability.

8.5.4 Imaging

The methods for assessment and recording are specified in the imaging charter.

The coded medical images will be used primarily for analysis as described in this protocol; however, the images may also be used for the development and evaluation of new analysis methods directly related to the area of research that this study covers.

8.5.5 Survival follow-up

For all randomized patients, follow-up for survival every 3 months until the end of study (defined as the last visit for the last patient randomized). If a patient misses a quarterly scheduled visit where survival status is required, or if the time-point does not align with a scheduled visit, survival status can be obtained via phone contact. For example, if regularly scheduled visits occur within 3 months of each other, no specific survival contact is needed. However, if the patient misses a visit, or if the visit is not scheduled for longer than 3 months, survival status may be collected via phone contact and should be entered on the appropriate CRF.

8.5.6 Other assessments

No additional tests will be performed on participants entered into this study.

9 Study discontinuation and completion

9.1 Discontinuation

9.1.1 Discontinuation of study treatment

The investigator must discontinue study treatment for a given participant if, he/she believes that continuation would negatively impact the participant's well-being.

A single tisagenlecleucel infusion may be discontinued if, in the investigator's opinion, its continuation would be detrimental to the patient's safety.

For patients randomized to Arm B (SOC) arm or patients who never receive tisagenlecleucel in Arm A, study treatment includes multiple lines of salvage immunochemotherapy as per local practice. Discontinuation of study treatment for a patient occurs when this study treatment is stopped earlier than the planned duration according to local guidelines and the approved drug label, and can be initiated by either the patient or the investigator.

Regardless of treatment arm, patients should NOT be considered withdrawn from treatment and primary follow-up, before they return for the safety follow-up visit, and the Month 60/EOT assessments indicated in [Section 9.2](#). If they fail to return for these assessments, every effort (e.g. telephone, email, letter) should be made to contact them.

Study treatment must be discontinued under the following circumstances

- Participant/guardian decision
- Pregnancy
- Use of prohibited treatment as per recommendations in the prohibited treatment section
- Any situation in which study participation might result in a safety risk to the participant
- Any AEs that in the judgment of the investigator, prevents the patient from continuing study treatment”
- Any laboratory abnormalities that in the judgment of the investigator, prevents the patient from continuing study treatment

If discontinuation of study treatment occurs, the investigator should make a reasonable effort to understand the primary reason for the participant’s premature discontinuation of study treatment and record this information.

Participants who discontinue study treatment or who decide they do not wish to participate in the study further should NOT be considered withdrawn from the study UNLESS they withdraw their consent (see withdraw of informed consent section). **Where possible, they should return for the assessments indicated** in the assessment schedule. If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone, e-mail, letter) should be made to contact the participant/pre-designated contact as specified in the lost to follow-up [Section 9.1.4](#). This contact should preferably be done according to the study visit schedule.

If the participant cannot or is unwilling to attend any visit(s), the site staff should maintain regular telephone contact with the participant, or with a person pre-designated by the participant. This telephone contact should preferably be done according to the study visit schedule.

After study treatment discontinuation, at a minimum, in abbreviated visits, the following data should be collected at clinic visits or via telephone/email contact:

- new / concomitant treatments
- adverse events/serious adverse events

The investigator must also contact the IRT to register the participant’s discontinuation from study treatment.

For patients who discontinue treatment for reasons other than documented disease progression, death, lost to follow-up, or withdrawal of consent, tumor assessments must continue to be performed as per the visit evaluation schedule until documented disease progression per BIRC, death, lost to follow-up, or withdrawal of consent.

9.1.2 Criteria for premature patient discontinuation from the study

Patients must be followed according to the visit schedule to ensure adequate data are collected for the proper assessment of study primary and secondary objectives.

All patients should be kept on study until the Month 60 visit whenever possible. It is anticipated that patients who received tisagenlecleucel treatment may discontinue from the primary follow-up (efficacy portion of the study) due to BIRC-confirmed disease PD/SD and only require the collection of key safety data in the long term additional follow-up. In cases where a patient discontinues without BIRC confirmed PD/SD, it may be possible for the patient to be followed for only key safety follow-up (without efficacy assessment) only after consultation and documented agreement with the Novartis medical monitor.

After 5 years of long term follow-up, patients who receive tisagenlecleucel will be asked to join the separate long term follow-up study (CCTL019A2205B). If patients move to the long term follow-up study, survival status should still be collected in this study until the end of study, defined as the last visit for the last patient randomized. The appropriate disposition eCRF should be recorded when the patient moves into the separate long term additional follow-up study and if the patient withdraws from the study prematurely.

Patients may voluntarily withdraw from the study or be withdrawn from the study at the discretion of the investigator at any time. Patients may also request to only be followed for survival at any time.

Patients may be withdrawn from the study if any of the following occur:

- The patient is lost to follow-up
- Patient noncompliance with study therapy and/or clinic appointments
- Voluntary withdrawal; a patient may remove himself/herself from the study at any time without prejudice.
- Termination of the study by the sponsor or the health authorities

9.1.3 Withdrawal of informed consent

Participants may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs only when a participant:

- Does not want to participate in the study anymore, and
- Does not allow further collection of personal data

In this situation, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for the participant's decision to withdraw his/her consent and record this information. Study treatment must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

Further attempts to contact the participant are not allowed unless safety findings require communicating or follow-up. All efforts should be made to complete the assessments prior to study withdrawal. A final evaluation at the time of the participant's study withdrawal should be made as detailed in the assessment table based on which phase of the study the patient is currently in (Primary Follow Up, Long term follow up, or Survival follow up).

Novartis will continue to keep and use collected study information (including any data resulting from the analysis of a participant's samples until their time of withdrawal) according to applicable law.

For US and Japan: All biological samples not yet analyzed at the time of withdrawal may still be used for further testing/analysis in accordance with the terms of this protocol and of the informed consent form.

For EU and RoW: All biological samples not yet analyzed at the time of withdrawal will no longer be used, unless permitted by applicable law. They will be stored according to applicable legal requirements.

9.1.4 Lost to follow-up

For participants whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator must show "due diligence" by documenting in the source documents steps taken to contact the participant, e.g. dates of telephone calls, registered letters, etc. A participant should not be considered as lost to follow-up until due diligence has been completed **or until the end of the study**.

9.1.5 Early study termination by the sponsor

The study can be terminated by Novartis at any time.

Reasons for early termination may include:

- Unexpected, significant or unacceptable safety risk(s) to patients enrolled in the study,
- Decision based on recommendation from applicable board(s) after review of safety and efficacy data
- Discontinuation of study drug development

In taking the decision to terminate, Novartis will always consider the participant welfare and safety. Should early termination be necessary, participants must be seen as soon as possible (provide instruction for contacting the participant, when the participant should stop taking drug, when the participant should come for a final visit) and the same assessments should be performed as described in [Section 8](#) for a discontinued or withdrawn participant. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the participant's interests. For participants who have received a tisagenlecleucel infusion, a long term post-study follow-up for lentiviral vector safety will still continue under a separate destination protocol for 15 years post infusion per health authority guidelines.

The investigator or sponsor depending on the local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

9.1.6 Criteria for stopping or pausing the study

The study will be paused, and health authorities notified if:

- Any participant develops detectable replication competent lentivirus (RCL) during the study
- The Sponsor, DMC (if applicable), or any regulatory body decides for any reason that participant safety may be compromised by continuing the study



- The Sponsor decides to discontinue the development of the intervention to be used in this study

The study may be paused pending notification of the health authorities and the DMC for investigation and possible protocol amendment if any participant experiences any of the following events within three weeks of the tisagenlecleucel cell infusion and re-infusion:

- Life-threatening (grade 4) toxicity attributable to protocol therapy that is unmanageable, unexpected and unrelated to chemotherapy and attributable to protocol therapy. High fevers, hypotension, hypoxia, disseminated intravascular coagulation, encephalopathy (e.g. lethargy, confusion, aphasia, seizure), ICU admission, dialysis and mechanical ventilation are expected. The expected adverse effects can also result in grade 4 liver toxicity, nephrotoxicity and cardiac dysfunction.
- Death suspected to be related to tisagenlecleucel therapy

9.2 Study completion and post-study treatment

All randomized patients should have a safety follow-up visit conducted 8 weeks after their last treatment administration or prior to starting another anticancer therapy, whichever occurs first. For ease of scheduling, the safety follow-up visit can occur as late as 9 weeks from their last treatment administration. The information collected is kept as source documentation. All SAEs reported during this time period must be reported as described in [Section 10.1.3](#). Patients should continue to be followed under the current protocol for key safety and survival, as per the survival follow-up in [Table 8-2](#), [Table 8-3](#), and [Table 8-4](#) and the long term additional follow-up schedule in [Table 8-2](#) and [Table 8-4](#). Survival assessments can be conducted via a form or telephone contact until last patient last visit (LPLV) as defined above.

The end of study is the when all participants have completed Month 60/EOT evaluation or were withdrawn prematurely, and any repeat assessments associated with this visit have been documented and followed-up appropriately by the Investigator, or in the event of an early study termination decision, the date of that decision. Participants who have completed their Month 60/EOT visit before the end of the study (defined as the last visit for the last patient randomized) will be followed every 3 months (q3m) until the end of the study for survival information, and will also be asked to join the separate LTFU study (CCTL019A2205B).

The primary analysis will occur when approximately 200 of EFS events is reached. At this time, the primary clinical study report (CSR) will be produced. After the primary analysis of EFS, the study will remain open provided the EFS demonstrates treatment benefit. If the primary analysis of EFS does not demonstrate treatment benefit, the follow-up for OS will end. Participants still being followed on the study after the primary analysis time point will continue as per the schedule of assessments. The study will end once the final OS analysis is performed when statistical significance is reached for OS analysis, see the statistical model, hypothesis, and method of analysis section) and the final analysis of study data is conducted. All available data from all participants up to this cutoff date will be analyzed.

At the time of the end of this study (defined as the last visit for the last patient randomized), participants continuing to derive benefit from the comparator treatment in the opinion of the Investigator may continue such treatment at the investigators discretion according to local clinical practice.

In addition, semiannual and annual evaluations will be performed for up to 15 years from the date of tisagenlecleucel infusion on all participants. Patients should be followed for the first 5 years on this protocol and an additional 10 years under a separate long term follow-up (LTFU) protocol as recommended by health authority guidance for participants treated with gene therapies. Patients who receive tisagenlecleucel will be asked to join a separate long term follow up study [CCTL019A2205B].

10 Safety monitoring and reporting

10.1 Definition of adverse events and reporting requirements

10.1.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (e.g., any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a participant or clinical investigation participant after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the infusion of tisagenlecleucel.

The investigator has the responsibility for managing the safety of individual participant and identifying adverse events.

Novartis qualified medical personnel will be readily available to advise on trial related medical questions or problems.

The occurrence of AEs must be sought by non-directive questioning of the participant at each visit during the study. Adverse events also may be detected when they are volunteered by the participant during or between visits or through physical examination findings, laboratory test findings, or other assessments.

Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate Adverse Event.

Adverse events must be recorded under the signs, symptoms or diagnosis associated with them, accompanied by the following information (as far as possible) (if the event is serious refer to [Section 10.1.2](#)):

1. the grade according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0, with the exception of CRS, which will follow [Table 4-2](#). If CTCAE grading does not exist for an AE, the severity of mild, moderate, severe, life-threatening and fatal, corresponding to Grades 1 - 5, will be used.
2. its relationship to the study treatment and other investigational treatment If the event is due to lack of efficacy or progression of underlying illness (i.e. progression of the study indication) the assessment of causality will usually be 'Not suspected'. The rationale for this guidance is that the symptoms of a lack of efficacy or progression of underlying illness are not caused by the trial drug, they happen in spite of its administration and/or

both lack of efficacy and progression of underlying disease can only be evaluated meaningfully by an analysis of cohorts, not on a single participant.

3. its duration (start and end dates) or if the event is ongoing, an outcome of not recovered/not resolved must be reported.
4. whether it constitutes a serious adverse events (SAE) (see [Section 10.1.2](#) for definition of SAE) and which seriousness criteria have been met.
5. action taken regarding with study treatment.

All adverse events must be treated appropriately. Treatment may include one or more of the following:

- Dose not changed
- Dose reduced/increased
- Drug interrupted/withdrawn

6. its outcome, i.e., its recovery status or whether it was fatal.

If the event worsens the event should be reported a second time in the eCRF noting the start date when the event worsens in toxicity. For AEs grade 3 and 4 only, if improvement to a lower grade is determined, a new entry for this event should be reported in the eCRF noting the start date when the event improved from having been Grade 3 or Grade 4.

Conditions that were already present at the time of informed consent should be recorded in medical history eCRF.

Adverse events (including laboratory abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms.

Adverse event monitoring should be continued for the duration as specified in [Section 10.1.1](#).

Once an AE is detected, it must be followed until its resolution or until it is judged to be permanent (e.g., continuing at the end of the study), and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study treatment, the interventions required to treat it, and the outcome. Non-fatal disease progression should not be reported as AE

Adverse events separate from the progression of malignancy (e.g., deep vein thrombosis at the time of progression or hemoptysis concurrent with finding of disease progression) will be reported as per usual guidelines used for such events with proper attribution regarding relatedness to the treatment.

Information about adverse drug reactions for tisagenlecleucel can be found in the [Tisagenlecleucel Investigator's Brochure], for drugs used for optional bridging chemotherapy, lymphodepleting chemotherapy and standard of care refer to the local label.

Abnormal laboratory values or test results constitute AEs only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms
- they are considered clinically significant
- they require therapy

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in participants with the underlying disease.

From the time of signing the ICF to the safety follow-up visit, all new or worsening AEs (including laboratory or test abnormalities deemed clinically significant by the investigator), regardless of causality will be recorded in the Adverse Events eCRF. Any AE, which started prior to the safety follow-up visit and is ongoing at the time of the visit, should continue to be followed until resolution. The primary safety analysis will occur using only those events which occur during this time period for both arms.

The safety follow-up visit should occur 8 weeks (56 days) after last treatment administration or prior to starting new anticancer therapy, whichever occurs first. After the safety follow-up visit, the collection of certain adverse events ([Section 16.3 Appendix 3](#)) through 5 years is required for all patients treated with tisagenlecleucel, while AEs are no longer reportable for patients who did not receive tisagenlecleucel. Patients in arm B who have the safety follow-up visit (indicating the end of AE collection), and then crossover to Arm A, should report from the time of the crossover visit to the next safety follow-up visit all new or worsening AEs (including laboratory or test abnormalities deemed clinically significant by the investigator), regardless of causality. After this next safety follow-up visit (as per [Table 8-4](#)), the collection of certain adverse events ([Section 16.3 Appendix 3](#)) through 5 years is required for all patients treated with tisagenlecleucel.

After 5 years (end of this study), patients who received tisagenlecleucel should be offered enrollment into long-term follow-up study CCTL019A2205B to monitor patients up to 15 years post tisagenlecleucel.

Detailed guidance on the reporting requirements for non-serious and serious AEs, in addition to concomitant medication and laboratory results during the relevant study period are provided in [Section 16.3 Appendix 3](#).

Detailed information regarding CRS adverse events (e.g. oxygen requirements, vasopressor usage) will be collected to allow for assessment using alternative CRS grading scales (e.g. ASTCT consensus grading).

10.1.2 Serious adverse events

An SAE is defined as any AE (appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s) or medical conditions(s) which meets any one of the following criteria:

- fatal
- life-threatening

Life-threatening in the context of a SAE refers to a reaction in which the participant was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (please refer to the ICH-E2D Guidelines).

- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect

- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
 - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
 - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
 - social reasons and respite care in the absence of any deterioration in the participant's general condition
 - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
- is medically significant, e.g. defined as an event that jeopardizes the participant or may require medical or surgical intervention to prevent one of the outcomes listed above

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the participant or might require intervention to prevent one of the other outcomes listed above. Such events should be considered as “medically significant”. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse.

All malignant neoplasms will be assessed as serious under “medically significant” if other seriousness criteria are not met and the malignant neoplasm is not a disease progression of the study indication.

Progression of malignancy with fatal outcome must be reported as an SAE within 24 hours of awareness, if the following criteria are met:

- Death within 30 days after tisagenlecleucel infusion, irrespective of causality to tisagenlecleucel
- Death beyond 30 days after tisagenlecleucel infusion, if there is at least a possible causality to tisagenlecleucel

Non-fatal disease progression should not be reported as SAE

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

All reports of intentional misuse and abuse of the product are also considered serious adverse event irrespective if a clinical event has occurred.

10.1.3 SAE reporting

To ensure participant safety, every SAE, regardless of causality, occurring after the participant has provided informed consent to Novartis safety within 24 hours of learning of its occurrence. The duration of this SAE reporting requirement is outlined in [Section 10.1.1](#). Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site.

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study treatment, a Chief Medical Office and Patient Safety (CMO&PS) Department associate may urgently require further information from the investigator for health authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same study treatment that this SAE has been reported.

Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

SAEs will be followed until resolution or until clinically relevant improvement or stabilization..

10.1.4 Adverse events of special reporting requirements

If specifically requested by a local Health Authority, expedited reporting of pre-specified AEs will occur. The initial SAE report will follow the local regulations/HA requirements (such as National Medical Products Administration (NMPA)) to be reported in timely manner.

10.1.5 Pregnancy reporting

If a female trial participant becomes pregnant, the study treatment should be stopped, and the trial participant must be asked to read and sign pregnancy consent form to allow the Study Doctor ask about her pregnancy.

To ensure participant safety, each pregnancy occurring after signing the informed consent must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. In case of live birth, the newborn should be followed up until 12 months of age to detect any developmental issue or abnormality that would not be seen at birth.

Pregnancy should be recorded and reported by the investigator to the Novartis Chief Medical Office and Patient Safety (CMO&PS). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to tisagenlecleucel infusion any pregnancy outcome. Any SAE experienced during pregnancy must be reported.

Pregnancy outcomes should be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.



10.1.6 Reporting of study treatment errors

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, participant or consumer (European Medicines Agency (EMA) definition).

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol.

Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

Study treatment errors and uses outside of what is foreseen in the protocol will be recorded on the appropriate CRF irrespective of whether or not associated with an AE/SAE and reported to Safety only if associated with an SAE.

Table 10-1 Guidance for capturing the study treatment errors including misuse/abuse

Treatment error type	Document in Dosing CRF (Yes/No)	Document in AE eCRF	Complete SAE form
Unintentional study treatment error	Yes	Only if associated with an AE	Only if associated with an SAE

For more information on AE and SAE definition and reporting requirements, please see the, respective sections.

10.2 Additional safety monitoring

10.2.1 Liver safety monitoring

To ensure participant safety and enhance reliability in determining the hepatotoxic potential of tisagenlecleucel, a standardized process for identification, monitoring and evaluation of liver events has to be followed.

The following two categories of abnormalities / adverse events have to be considered during the course of the study (irrespective of whether classified/reported as AE/SAE):

- Liver laboratory triggers, which will require repeated assessments of the abnormal laboratory parameter
- Liver events, which will require close observation, follow-up monitoring and contributing factors are recorded on the appropriate CRFs

Please refer to [Table 16-7](#) in [Section 16.4](#) for complete definitions of liver laboratory triggers and liver events.

Every liver event defined in [Table 16-7](#) should be followed up by the investigator or designated personnel at the trial site, as summarized below. Additional details on actions required in case of liver events are outlined in [Table 16-8](#). Repeat liver chemistry tests (ALT, AST, TBILI, PT/INR, ALP and gamma glutanyl transferase (GGT)) to confirm elevation.

- These liver chemistry repeats will be performed using the central laboratory. If results will not be available from the central laboratory, then the repeats can also be performed at a

local laboratory to monitor the safety of the participant. If a liver event is subsequently reported, any local liver chemistry tests previously conducted that are associated with this event should have results recorded on the appropriate CRF

If the initial elevation is confirmed, close observation of the participant will be initiated, including consideration of treatment interruption if deemed appropriate.

- Discontinuation of the investigational drug (refer to the Discontinuation of study treatment [Section 9.1.1](#)), if appropriate
- Hospitalization of the participant if appropriate
- Causality assessment of the liver event
- Thorough follow-up of the liver event, which can include based on investigator's discretion:
 - Serology tests, imaging (e.g., such as abdominal ultrasound (US), CT or MRI, as appropriate) and pathology assessments, gastroenterologist's or hepatologist's consultancy; obtaining more detailed history of symptoms and prior or concurrent diseases, history of concomitant drug use, exclusion of underlying liver disease, obtaining a history of exposure to environmental chemical agents.

All follow-up information, and the procedures performed must be recorded as appropriate in the CRF.

10.2.2 Renal safety monitoring

The following two categories of abnormal renal laboratory values have to be considered during the course of the study:

- Serum creatinine increase $\geq 25\%$ compared to baseline during normal hydration status
- Urine protein-creatinine ratio (PCR) $\geq 1\text{g/g}$ or $\geq 100\text{ mg/mmol}$, OR new onset dipstick proteinuria $\geq 3+$ OR new onset dipstick hematuria $\geq 3+$ (after excluding menstruation, urinary tract infection, extreme exercise, or trauma)

Renal event findings must be confirmed 24-48 hours after the first assessment (*select as applicable*: for Phase 1 and early Phase 2) OR after ≥ 24 hours but ≤ 5 days after first assessment (*select as applicable*: for Phase 2 and Phase 3).

Every renal laboratory trigger or renal event as defined in [Table 16-9](#) should be followed up by the investigator or designated personnel at the trial site as summarized in [Table 16-9](#).

10.2.3 Data Monitoring Committee

This study will include a data monitoring committee (DMC) which will function independently of all other individuals associated with the conduct of this clinical trial, including the site investigators participating in the study. The DMC will assess at defined intervals the progress and safety data of the clinical trial, and recommend to the sponsor whether to continue, modify or terminate a trial.

Specific details regarding composition, responsibilities, data monitoring and meeting frequency, and documentation of DMC reports, minutes, and recommendations will be described in a separate charter that is established between the sponsor and the DMC.

10.2.4 Steering committee

The steering committee (SC) will be established comprising investigators participating in the trial, Novartis representatives from the Clinical Trial team and not members of the DMC. The SC will ensure transparent management of the study according to the protocol through recommending and approving modifications as circumstances require. The SC will review protocol amendments as appropriate. Together with the clinical trial team, the SC will also develop recommendations for publications of study results including authorship rules. The details of the role of the Steering Committee will be defined in a Steering Committee charter.

10.2.5 Blinded independent review committee (BIRC)

A BIRC will be established to review data related to disease response assessments during the study, before randomization and determine response and relapse for the primary analysis. A BIRC charter will detail the BIRC data flow and review process in alignment with the response definitions in [Section 16.2 Appendix 2](#). Patient management will be based upon local investigator assessments except for the eligibility crossover. The designation of response and relapse for the primary analysis and other related secondary efficacy endpoints will be based on the evaluations made by the BIRC. Details regarding the constitution of the BIRC and its specific roles will be documented in the BIRC charter and agreed upon between Novartis and the BIRC before initiation of any BIRC review.

10.2.6 Follow up of secondary malignancy

For patients treated with tisagenlecleucel, treating physician/ healthcare providers should contact Novartis if the patient develops a secondary malignancy. Upon clinical confirmation secondary malignancy, blood samples should be collected for CAR transgene and RCL cellular kinetic analysis. (For patients enrolled in China, blood samples are not to be collected unless approval has been obtained by all relevant Chinese authorities).

Novartis strongly recommends collection of biopsy samples from secondary malignancies (if applicable and previously collected as standard of care in diagnosing or treating the secondary malignancy) for analysis, such as CAR-transgene and RCL. (For patients enrolled in China, biopsy samples are not to be collected). Additional details for sample handling and shipping are outlined in the [\[CCTL019H2301 Laboratory Manual\]](#).

11 Data collection and database management

11.1 Data collection

Designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRF). The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements, Investigator site staff will not be given access to the electronic data capture (EDC) system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs, allow modification and/or verification of the entered data by the investigator staff.

The investigator/designee is responsible for assuring that the data (recorded on CRFs) (entered into eCRF) is complete, accurate, and that entry and updates are performed in a timely manner. The Investigator must certify that the data entered are complete and accurate

After final database lock, the investigator will receive copies of the participant data for archiving at the investigational site.

All data should be recorded, handled and stored in a way that allows its accurate reporting, interpretation and verification.

11.2 Database management and quality control

Novartis personnel (or designated CRO) will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.

Concomitant treatments and prior medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical (ATC) classification system. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Randomization codes will be tracked using an Interactive Response Technology (IRT). The system will be supplied by a vendor, who will also manage the database. The data will be sent electronically to Novartis at specific timelines.

Once all the necessary actions have been completed and the database has been declared to be complete and accurate, it will be locked. Any changes to the database after that time can only be made after written agreement by Novartis development management.

11.3 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and data capture requirements (i.e. eSource DDE or eCRFs) with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of participant records, the accuracy of data capture / data entry, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized Novartis/ CRA organization. Additionally, a central analytics organization may analyze data & identify risks & trends for site operational parameters, and provide reports to Novartis clinical teams to assist with trial oversight.

The investigator must maintain source documents for each participant in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the

participant's file. The investigator must also keep the original informed consent form signed by the participant (a signed copy is given to the participant).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, adherence to PRO assessment, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the participants will be disclosed.

12 Data analysis and statistical methods

It is planned that the data from all centers participating in the trial will be combined, so that an adequate number of participants are available for analysis. Novartis and/or a designated CRO will perform the final EFS analyses. Any data analyses performed independently by any investigator should be submitted to Novartis before publication or presentation.

The global study main cohort primary efficacy and safety analyses will be performed after approximately 200 EFS events have been documented by BIRC from the global study main cohort. Following the primary analysis for EFS, the study will remain open. Participants still being followed on the study will continue as per the schedule of assessments.

Data for the participants from China mainland randomized in the global study prior to completion of global recruitment will be part of the global primary efficacy and safety analysis. Data for the entirety of participants from the global study main cohort and China extension cohort (i.e., the China patients in the global study main cohort and the additional patients from China extension cohort) will be analyzed separately and submitted to the Chinese regulatory authority once approximately 18 EFS events have been documented by the BIRC in Chinese participants. All definitions in Section 12 apply to both the global study and the analysis of Chinese participants from the global study main cohort and China extension cohort unless otherwise specified. At the time of analysis of patients from China mainland, supportive analyses will also be conducted including Chinese patients recruited from approved sites in Taiwan and Hong Kong.

The study will end once the final OS analysis is performed at approximately 5 years from the 1st patient randomized to the study, or earlier, if statistical significance is reached at the interim analysis for OS at the time of the primary analysis of EFS, at which point the final CSR will be published. All available OS and safety data from all patients up to this cutoff date will be analyzed.

Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

12.1 Analysis sets

The analysis sets to be used are defined below.



12.1.1 Screened Set

The Screened Set comprises all patients who have signed informed consent and were screened in the study.

12.1.2 Infused Set

The Infused set comprises all participants who received infusion of tisagenlecleucel. The Infused set will be used for efficacy and safety summaries of participants infused with tisagenlecleucel.

12.1.3 Full Analysis Set

The Full Analysis Set (FAS) comprises all patients to whom study treatment has been assigned by randomization. According to the intent to treat principle, patients will be analyzed according to the treatment and strata they have been assigned to during the randomization procedure.

The Full Analysis Set (FAS) will be used as the main analysis set for efficacy, demographics and other baseline characteristics.

12.1.4 Safety Set

The Safety Set includes all patients to whom study treatment has been assigned by randomization. The Safety set will be used for all randomized safety comparisons. Please note in this study, the Safety set is the same as the FAS.

12.1.5 Per-Protocol Set

The Per-Protocol Set (PPS) consists of a subset of patients in the FAS who are compliant with requirements of the clinical study protocol (CSP).

Protocol deviations leading to exclusion from the PPS include:

- Diagnosis of disease other than histologically confirmed, aggressive B-cell NHL at relapse /progression or PR after front line therapy (inclusion criterion #3);

The detailed exclusion criteria of PPS will be determined and documented in the study Statistical Analysis Plan (SAP).

12.1.6 Cellular Kinetic Analysis Set

The tisagenlecleucel cellular kinetic analysis set (CKAS) consists of patients in the FAS who have received one dose of tisagenlecleucel and have at least one evaluable cellular kinetic parameter. The CKAS will be used for summaries (tables and figures) of cellular kinetic data.

12.2 Participant demographics and other baseline characteristics

Demographic and other baseline data will be listed and summarized descriptively by treatment arm for the FAS.

Categorical data will be presented as frequencies and percentages. For continuous data, summary statistics will be presented (i.e., including mean, standard deviation, median,



minimum, and maximum). For selected parameters, 25th and 75th percentiles will also be presented.

Relevant medical histories and current medical conditions at baseline will be summarized by system organ class and preferred term, by treatment arm. Number and percentage of patients who received prior anti-neoplastic medications/therapies will be summarized. Patients will be classified by their prior treatment response.

12.3 Treatments

The Safety set will be used for the analyses below. Categorical data will be summarized as frequencies and percentages. For continuous data, mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum will be presented.

For patients who received tisagenlecleucel infusion, the total cells infused (cells) and total tisagenlecleucel transduced viable T cells infused (cells) will be listed and summarized using descriptive statistics. Patients will be categorized as below, within or above the prescribed dose range.

For patients who received standard of care therapy, the medication name, length of therapy and total dose will be listed and summarized using descriptive statistics.

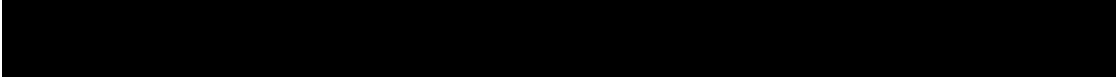
Concomitant medications and significant non-drug therapies prior to and after the start of tisagenlecleucel infusion or SOC treatment(s) will be listed by patient and summarized by the Anatomical Therapeutic Chemical (ATC) term classification system, by treatment arm. Lymphodepleting chemotherapies will be listed and summarized. Transfusion during the study will be listed. In addition, anti-cytokine medications for the management of CRS will be summarized.

12.4 Analysis of the primary endpoint

The primary aim of the study is to compare two second line treatment strategies in adult patients with aggressive B-cell non-Hodgkin lymphoma who are refractory to or relapsed after frontline standard of care and are eligible for stem cell transplantation. The treatment strategies will be compared based on their effect on delaying the composite event of disease progression / stable disease at or after the week 12 assessment or death at any time. These two treatment strategies will be compared based on all randomized patients, irrespective of whether the patient received all or some of the components of the randomized treatment. Intercurrent events preventing compliance with these strategies such as initiation of alternative cancer therapies prior to the composite event of interest, will be handled accordingly. A Cox regression model stratified by randomization stratification factors will be used to estimate the hazard ratio (HR) of EFS.

12.4.1 Definition of primary endpoint

The primary endpoint of the study is event-free survival (EFS), defined as the time from the date of randomization to the date of the first documented disease progression or stable disease at or after the week 12 assessment, as assessed by BIRC per Lugano criteria (see [Section 16.2 Appendix 2](#) for further details), or death due to any cause, at any time. Censoring conventions are provided in [Section 12.4.3](#).



12.4.2 Statistical model, hypothesis, and method of analysis

The following statistical hypothesis will be tested to address the primary efficacy objective:

$H_{01}: \theta_1 \geq 1$ vs. $H_{A1}: \theta_1 < 1$ where θ_1 is the hazard ratio (tisagenlecleucel arm vs. SOC arm) of EFS. The primary efficacy analysis to test this hypothesis will be conducted using a stratified log-rank test at the one-sided 2.5% level of significance. The stratification will be based on the randomization stratification factors, i.e., remission duration (refractory to front line therapy or relapsed <6 months vs. relapsed at 6 - 12 months), IPI score (<2 vs. ≥ 2) ([The International Non-Hodgkin's Lymphoma Prognostic Factors Project 1993](#); [Moskowitz 1999](#)), and region (North America vs. Rest of World).

The analysis of EFS will be based on the FAS according to the randomized treatment arm and strata assigned at randomization. The distribution of EFS will be estimated using the Kaplan-Meier method. Kaplan-Meier curves, medians and 95% confidence intervals of the medians will be presented for each treatment arm. The hazard ratio for EFS will be calculated, along with its 95% confidence interval, from a stratified Cox model using the same stratification factors as for the log-rank test.

There will be no interim analysis for EFS. The analysis for EFS in the FAS will be performed after approximately 200 EFS events have been documented by the BIRC.

The primary analysis of EFS for Chinese participants will be based on Chinese participants in the FAS of the global study as well as Chinese participants to whom study treatment has been assigned by randomization in the China extension cohort. The analysis will be performed after 18 EFS events have been observed in Chinese participants. The analysis will be conducted as for the global cohort, except that the log-rank test will not be performed and the region stratification factor is not applicable.

12.4.3 Handling of missing values/censoring/discontinuations

If no EFS event is observed prior to the earliest censoring event, EFS will be censored at the date of the last adequate assessment prior to the earliest censoring event. The censoring events include lost to follow-up, withdrew consent, analysis cut-off, and initiation of new cancer therapy.

The following scenarios after randomization will be considered as initiation of new cancer therapy and EFS will be censored:

In tisagenlecleucel arm,

- start any anti-CD19 or gene therapy other than tisagenlecleucel,
- start conditioning therapy with intention of HSCT
- start any anti-neoplastic therapy at any time after tisagenlecleucel infusion
- start any anti-neoplastic therapy other than optional bridging therapy or lymphodepleting chemotherapy prior to tisagenlecleucel infusion (including for patients who do not go on to receive tisagenlecleucel)

In the SOC arm,

- start anti-CD19 or gene therapy including tisagenlecleucel

- start any anti-neoplastic therapy other than protocol allowed SOC treatment options prior to HSCT (including for patients who do not go to HSCT)
- start of any anti-neoplastic therapy at any time after HSCT

12.4.4 Sensitivity and supportive analyses

Due to the delay between randomization and tisagenlecleucel infusion, a weighted log rank test may be used as a sensitivity analysis. For example a piecewise weighted log-rank test (e.g., assigning weights of 0 to event times in the delayed period and weights of 1 thereafter), or Fleming-Harrington (FH) weighted log-rank test (e.g. FH (0,1) to assign more weight to later events) etc. The exact weights to be used will be defined in the statistical analysis plan

The hazard ratio and 95% confidence interval for EFS per BIRC assessment based on:

- An unstratified and covariate unadjusted Cox model.
- A stratified and covariate adjusted Cox model including as covariates the following: (age, race, gender, etc.)

EFS as per investigator assessment will be analyzed using a stratified Cox model, with the same analysis conventions as the primary efficacy analysis, and the treatment effect will be summarized by the hazard ratio with its 95% confidence interval. Kaplan-Meier curves, medians and 95% confidence intervals of the medians will be presented for each treatment group.

The following two supportive analyses will also be performed:

- EFS per BIRC irrespective of new anti-cancer therapy for lymphoma, i.e., EFS events will be counted even if occurring after start of a new anti-cancer therapy. This corresponds to a fully intention-to-treat approach for both treatment strategies.
- EFS per BIRC considering new anti-cancer therapy for lymphoma at any time as an EFS event.

Depending on the amount of missing assessments, further sensitivity analyses may be considered, for example, if an EFS event is observed after two or more missing or non-adequate tumor assessments, then EFS will be censored at the last adequate assessment before the EFS event.

These analyses will include Kaplan-Meier medians with their 95% confidence intervals, and summarized by hazard ratio with its 95% confidence interval.

EFS per BIRC review will be analyzed based on the Per Protocol Set, using the same analysis conventions as in the primary efficacy analysis (with the exception of the log-rank test, which will not be performed).

If the primary analysis is statistically significant, subgroup analyses to assess the homogeneity of the treatment effect across demographic and baseline disease characteristics will be performed based on the following:

- Remission duration (refractory to front line therapy or relapsed <6 months vs. relapsed 6 - 12 months)
- IPI score (<2 vs. ≥2)



- Region (North America vs. Rest of World)
- Age: <65 years, ≥ 65 years
- Gender: Male, Female
- Race: Asian, Black, Caucasian, Other,
- Ethnicity: Hispanic or Latino, Chinese, Indian, Japanese, Mixed ethnicity, Other
- Prior response status: Primary refractory, relapsed
- Histology: e.g. DLBCL, NOS, FL3B, Other
- Disease stage at study entry: I/II vs III/IV
- DLBCL cell of origin subtype: GCB, ABC, Other
- Rearrangements in MYC/BCL2/BCL6 genes: Double/Triple hits, Other

The analyses will include Kaplan-Meier summaries and hazard ratios (together with associated 95% CI) from stratified Cox models. Subgroup analyses will only be performed if adequate number of events are observed.

The number of participants censored and reasons for censoring will be summarized by treatment group using descriptive statistics, presented separately for local review and BIRC.

12.5 Analysis of secondary endpoints

The secondary objectives in this study are to compare the two treatment groups with respect to overall survival (OS), and to evaluate the overall response rate (ORR), duration of response (DOR), time to response (TTR), PRO, and safety.

There are no key secondary endpoints in this study.

Overall survival (OS), defined as time from the date of randomization to date of death due to any cause, will only be formally tested between the two treatment arms, if the primary endpoint (EFS by BIRC) is significant.

Testing of the null hypothesis, that the survival functions for OS in the two arms are identical, will be conducted by stratified log-rank tests in the FAS as part of a group sequential design with two looks. The interim analysis of OS will be at the time of the primary analysis for EFS, and the final analysis will be 5 years after randomization of the first patient if OS is not significant at the time of primary analysis. A Haybittle-Peto boundary will be used, where the one-sided significance level is 0.05% at the interim analysis and 2.5% at the final analysis. The stratification will be based on the randomization stratification factors, i.e., remission duration (refractory to front line therapy or relapsed <6 months vs. relapsed 6 - 12 months), IPI score (<2 vs. ≥2) and region (North America vs. Rest of World).

Patients in SOC arm are eligible to cross over to tisagenlecleucel treatment, after BIRC-confirmed progression of disease or continuation of stable disease at or after the week 12 assessment up until one year after HSCT. The primary analysis of OS will be based on the intent-to-treat (ITT) population, i.e., patients randomized to SOC arm who cross over to tisagenlecleucel arm will be considered to be in the SOC arm for OS analysis. As a sensitivity analysis, methods of analysis of OS accounting for crossover (for example, rank preserving structural failure time model and inverse probability of censoring weights) will be considered.

If death has not been observed by the date of analysis cutoff, OS will be censored at the date of last contact.

Distribution of OS will be estimated using the Kaplan-Meier method. The median OS and the proportion of patients alive at 6, 12 weeks, 6, 12, 18, 24, 36, 48 and 60 months with 95% confidence intervals will be presented by treatment arms. The hazard ratio (HR) of OS will be summarized along with 95% confidence interval.

12.5.1 Efficacy and/or pharmacodynamic endpoints

BIRC assessment as well as investigator assessment will be used for the analysis of secondary endpoints that involve disease response. Specifications below are described for BIRC, and the same analyses will be repeated for investigator, unless specified otherwise.

12.5.1.1 Overall response rate (ORR)

Overall response rate (ORR) is defined as the proportion of participants with best overall response (BOR) of complete response (CR) or partial response (PR) on or after the Week 12 assessment, as per BIRC and according to the Lugano criteria (see [Section 16.2 Appendix 2](#) for details).

ORR and its 95% confidence interval will be presented by treatment arm in the FAS. As a sensitivity analysis, ORR as per investigator assessment will be presented by treatment group, along with 95% confidence intervals. A further sensitivity analysis for ORR will be performed in the tisagenlecleucel arm using evidence of disease at the Week 6 assessment (i.e., after the end of bridging chemotherapy). A descriptive summary of patients' disease response status at the Week 6 assessment will also be provided.

12.5.1.2 Duration of response (DOR)

Duration of response (DOR) only applies to patients whose best overall response is complete response (CR) or partial response (PR) according to Lugano criteria based on disease response data per BIRC. It is defined as the time from the date of first documented response of CR or PR to the date of first documented progression (SD or PD at or after the week 10 will be considered progression) or death due to aggressive B-cell NHL.

In case a patient does not have progression or death due to aggressive B-cell NHL prior to data cutoff, DOR will be censored at the date of the last adequate assessment on or prior to the earliest censoring event. The same censoring reasons and censoring date options used in the primary EFS analysis will be used for DOR, with the addition of death due to reason other than aggressive B-cell NHL.

The distribution of DOR will be estimated using the Kaplan-Meier method. Kaplan-Meier curves, medians and 95% confidence intervals of the medians will be presented for each treatment arm. The hazard ratio for DOR will be calculated, along with its 95% confidence interval, from a stratified Cox model using the randomization stratification factors.

As a sensitivity analysis, distribution of DOR will also be estimated using the Kaplan-Meier method in which death due to reason other than aggressive B-cell NHL will be included as an event.

12.5.1.3 Time to response (TTR)

Time to overall disease response (CR or PR) is defined as time from the date of randomization to the date of first documented overall disease response of PR or CR according to Lugano criteria based on disease response data per BIRC on or after the Week 12 assessment.

The TTR analysis will be based on the ITT population, i.e., patients randomized to SOC arm who cross over to tisagenlecleucel arm will be considered to be in the SOC arm.

TTR will be censored for patients who did not achieve a PR or CR:

- At maximum follow-up (i.e. FPFV to LPLV used for the analysis) for patients who died due to any cause, progressed on or after the week 12 assessment, or initiated new anticancer therapy (as defined in [Section 12.4.3](#)),
- At the date of the last adequate assessment otherwise.

TTR will be estimated using the Kaplan-Meier method and the median time to response will be presented along with a 95% confidence interval. As a sensitivity analysis, TTR as per investigator assessment will be presented by treatment group, along with 95% confidence intervals.

12.5.2 Safety endpoints

For all safety analyses, the safety set will be used, unless otherwise specified. All listings and tables will be presented by treatment arms.

The overall observation period will be divided into three mutually exclusive segments:

1. Pre-treatment period: from day of participant's informed consent to the day before randomization.
2. Safety comparison period: from day of randomization to the earlier of:
 - 56 days after last dose of study treatment
 - Start date of new cancer therapy other than assigned treatment
3. Post-safety comparison period: after end of safety comparison period until end of study

Primary safety summaries (tables, figures) by treatment arms include only data from the safety comparison period with the exception of baseline data which will also be summarized where appropriate (e.g. change from baseline summaries). All safety data will be summarized and listed by treatment period.

Please note that patients crossed over from arm B to arm A will be considered as having started new cancer therapy other than assigned treatment and therefore will not be included in the primary safety summaries.

In addition, safety data after tisagenlecleucel infusion will be separately summarized (including patients received tisagenlecleucel infusion in either arm A or patients crossed-over from arm B) for the post-infusion period, defined as from day of tisagenlecleucel infusion until end of study.

Adverse events

For randomized safety comparison, all information obtained on adverse events will be displayed by treatment arm and patient.



The number (and percentage) of patients with treatment emergent adverse events will be summarized in the following ways:

- by treatment, primary system organ class and preferred term.
- by treatment, primary system organ class, preferred term and maximum severity.

Summary tables for adverse events will be provided for AEs that started or worsened during the safety comparison period. All safety data will be listed by reporting period.

The incidence of adverse events during the safety comparison period will be summarized by primary system organ class (SOC), preferred term, severity (based on CTCAE grades), and relation to study treatment by treatment arm. The frequency of Common Toxicity Criteria (CTC) grade 3 and 4 AEs will be summarized separately.

Separate summaries will be provided for study medication related adverse events, death, serious adverse events, other significant adverse events leading to discontinuation.

The number (and proportion) of patients with adverse events of special interest (AESI) will be summarized by treatment. The current search criteria of AESI are based on limited experience from ongoing clinical studies without an accurate assessment of causality. AESI and the search criteria of AESI will be updated prior to reporting. AESI that occur within 8 weeks of the tisagenlecleucel infusion will be summarized by group term and preferred term.

A patient with multiple adverse events within a primary system organ class is only counted once towards the total of the primary system organ class.

Adverse events which will be counted for a specific treatment period are those which are treatment-emergent. These events are those with an onset after the start of the treatment period, or which were present prior to the start of the treatment period but increased in severity, changed from being not suspected to being suspected of study drug relationship, or developed into SAEs after the start of the treatment period.

The incidence of treatment-emergent adverse events (new or worsening from baseline) will be summarized by system organ class and or preferred term, severity (based on CTCAE grades), type of adverse event, relation to study treatment.

Serious adverse events, non-serious adverse events and adverse events of special interest (AESI) during the safety comparison period will be tabulated.

All AEs, deaths and serious adverse events (including those from the pre and post-treatment periods) will be summarized and listed and those collected during the pre-treatment and post-safety comparison period will be flagged.

In addition, safety data after tisagenlecleucel infusion will be separately summarized. The AE summaries will include all AEs that started or worsened during the post-infusion period, i.e. the ***tisagenlecleucel-treatment-emergent*** AEs.

CRS grades will be primarily reported according to the Lee criteria ([Table 4-2](#))([Lee et al 2014](#)) and neurological events will be reported according to the CTCAE v5.0. Additionally, CRS and neurotoxicity will also be assessed using other grading scales (e.g. ASTCT consensus grading) and a sensitivity analysis will be conducted.



Vital signs

All vital signs data will be listed by treatment group, patient, and visit and if ranges are available, abnormalities will be flagged. Summary statistics will be provided by treatment.

12-lead ECG

12-lead ECGs including PR, QRS, QT, QTcF intervals and heart rate (HR) will be obtained for each patient during the study. ECG data will be read and interpreted locally.

Categorical Analysis of QT/QTc interval data based on the number of patients meeting or exceeding predefined limits in terms of absolute QT/QTc intervals or changes from baseline will be presented. In addition, a listing of these patients will be produced by treatment arm.

All ECG data will be listed by treatment arm, participant and visit, abnormalities will be flagged. Summary statistics will be provided by treatment and visit.

Clinical laboratory evaluations

Grading of laboratory values will be assigned programmatically as per NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5. The calculation of CTCAE grades will be based on the observed laboratory values only, clinical assessments will not be taken into account.

CTCAE Grade 0 will be assigned for all non-missing values not graded as 1 or higher. Grade 5 will not be used.

For laboratory tests where grades are not defined by CTCAE v5, results will be categorized as low/normal/high based on laboratory normal ranges.

The following summaries will be generated separately for hematology, and biochemistry tests by treatment arm:

For laboratory tests where grades are defined by CTCAE v5

- Worst post-baseline CTCAE grade (regardless of the baseline status). Each patient will be counted only once for the worst grade observed post-baseline.
- Shift tables using CTCAE v5 grades to compare baseline to the worst value during safety comparison period for SOC and to compare baseline to the worst post-infusion value for tisagenlecleucel arm

For laboratory tests where grades are not defined by CTCAE v5,

- Shift tables using the low/normal/high/ (low and high) classification to compare baseline to the worst value during safety comparison period.

Listing of all laboratory data with values flagged to show the corresponding CTCAE v5 grades if applicable and the classifications relative to the laboratory normal ranges.

In addition to the above mentioned tables and listings, other exploratory analyses, for example figures plotting time course of raw or change in laboratory tests over time or box plots might be specified in the Statistical Analysis Plan (SAP).



Other safety evaluations

Presence of detectable RCL will be tested by VSV-G at scheduled assessments. If blood samples for RCL testing are negative through Month 12, all samples taken after Month 12 will be stored for potential future testing. All safety data will be listed.

Safety subgroup analysis

Key safety summaries for adverse events regardless of relationship to study drug by System, Organ, Class (SOC) and PT, and adverse events of special interest will be repeated on the Safety Set in the following subgroups of age, gender, race, ethnicity, histology, and DLBCL cell of origin subtype subgroups.

Summary tables will only be performed if at least 5 patients are present in each subgroup. Some grouping of classes will be considered.

Immunogenicity

The humoral immunogenicity assay measures the antibody titers specific to the tisagenlecleucel molecule prior to and following infusion. Data will be further fractionated to determine proportion of participants who make transient versus sustained antibody responses. The cellular immunogenicity assay assesses the presence of T lymphocytes activated by the tisagenlecleucel protein. Data will be reported as summary statistics of pre and post-dose levels of activated T lymphocytes. Cellular kinetic parameters, efficacy and concentration time profiles will be summarized according to pre-existing and treatment-induced immunogenicity categories in Arm A and patients who have crossed over to tisagenlecleucel.

Resource utilization

Data relating to resource utilization will be used for the purpose of economic evaluation and will be carried out and reported as a separate activity.

Hospitalizations will be evaluated in this study as an exploratory endpoint to characterize the impact of study treatment on this aspect of healthcare resource utilization. In addition, these data may be used to support assessments used to characterize the economic impact of study treatment regimens. Hospitalization data of interest will focus on those hospitalizations reported within the first 6 months after randomization.

Hospitalizations as a result of the following reasons are not to be reported:

- Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
- Social reasons and respite care in the absence of any deterioration in the participant's general condition
- Treatments occurring on an emergency outpatient basis that does not result in hospital admission and involves an event not fulfilling any of the definitions of a SAE as described in [Section 10.1.2](#) are not required.

Healthcare resource utilization data regarding hospitalizations should be captured from randomization (Day 1) up to Month 6 for the participant as described in [Table 8-2](#) and [Table 8-3](#).

12.5.3 Patient reported outcomes

PRO data from FACT-Lym, EQ-5D-5L and the SF-36 v2 (Acute form) will be assessed during the study as indicated in [Table 8-1](#), [Table 8-2](#), [Table 8-3](#), and [Table 8-4](#). Summary scores will be generated by summing the item responses on the questions for each domain in accordance with the respective scoring manual provided by the developers. Descriptive statistics (e.g. mean, median and frequency) and change from baseline of the summary scores for each post baseline time-point/window of assessment will be provided by treatment arm (tisagenlecleucel and SOC) and crossover, respectively. FAS will be used for all analysis.

For each treatment group and at each time point, the number and percentage of patients who complete the SF-36 v2, FACT-Lym, and EQ5D will be summarized in a table.

12.5.3.1 SF-36 v2

The SF-36 comprises 36 questions, which can be summarized in eight health domain scores and further combined into a physical component summary (PCS) and a mental component summary (MCS) score. Domain and component summary scores will be converted to norm-based scores based on the general population. A higher SF-36 score denotes better quality of life.

Summary statistics will be reported for each of domains and components over time by treatment arm. Repeated measures mixed-effects model will be carried to compare the two groups with respect to the change from baseline.

Time to definitive deterioration for PCS and MCS will be summarized using Kaplan-Meier methods. Time to definitive deterioration is defined as the time from randomization to the earliest time when the patient's score shows at least 3 points or higher decrease from baseline (with no later change below this threshold). Time to definitive deterioration in each of the eight health domain will also be analyzed. The log-rank test will be used to compare the time to definitive deterioration between the two treatment groups. Rates of improvement for PCS and MCS will be evaluated from baseline to each time point and will be compared between the two treatment groups using chi-square test. Improvement is defined as increase of at least 3 points for PCS and MCS ([Swigris et al 2010](#); [Oerlemans et al 2011](#); [Mehta et al 2017](#)).

12.5.3.2 FACT-Lym

Functional Assessment of Cancer Therapy-Lymphoma (FACT-Lym) is an extension of the FACT-General (FACT-G) standardized assessment of patients that includes the lymphoma subscale (FACT-LymS). The FACT-G is divided into 4 domains: physical, social/family, emotional, and functional well-being. The FACT-LymS is an additional 15 questions meant to evaluate response to treatment and symptoms associated with lymphoma. The FACT-Lym also includes the trial outcome index (FACT-Lym TOI) and the total score (FACT-Lym TS).

Summary statistics will be reported for each of scales over time by treatment arm. Repeated measures mixed-effects model will be carried to compare the two groups with respect to the change from baseline for FACT-G total score, FACT-LymS, FACT-Lym TOI and FACT-Lym TS.

Time to definitive deterioration for FACT-G total score (≥ 3 decrease), FACT-LymS (≥ 2.9 decrease), FACT-Lym TOI (≥ 5.5 decrease) and FACT-Lym TS (≥ 6.5 decrease) will be

summarized using Kaplan-Meier methods. Time to definitive deterioration is defined as the time from randomization to the earliest time when the patient's score shows the above decrease from baseline (with no later change below this threshold). The log-rank test will be used to compare the time to first deterioration between the two treatment groups.

Rates of improvement for these four scores will be evaluated from baseline to each time point and will be compared between the two treatment groups using chi-square test. Improvement is defined as increase of at least 3 points, 2.9 points, 5.5 points, and 6.5 points for FACT-G total score, FACT-LymS, FACT-Lym TOI, and FACT-Lym TS respectively ([Webster et al 2003](#); [Carter et al 2008](#)).

12.5.3.3 EQ-5D-5L

The EQ-5D-5L questionnaire consists of the EQ-5D descriptive system and a visual analogue scale (the EQ-VAS). The EQ-5D descriptive system measures a patient's health state on 5 dimensions which include: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The respondent's self-rated health is assessed on a scale from 0 (worst imaginable health state) to 100 (best imaginable health state) by the EQ-VAS.

Summary statistics will be reported for EQ-VAS over time by treatment arm. Repeated measures mixed-effects model will be carried to compare the two groups with respect to the change from baseline.

Time to definitive deterioration for EQ-VAS is defined as the time from randomization to the earliest time when the patient's score shows at least 7 points or higher decrease from baseline (with no later change below this threshold). The log-rank test will be used to compare the time to first deterioration between the two treatment groups.

Rates of improvement for EQ-VAS will be evaluated from baseline to each time point and will be compared between the two treatment groups using chi-square test. Improvement is defined as increase of at least 7 points ([Kantarjian et al 2016](#))

For the EQ-5D health state profiles, the proportions of patients reported having "no", "slight", "moderate", "severe", or "extreme" problems at each time point will be reported for each of the 5 dimensions.

12.5.4 Cellular kinetics

Tisagenlecleucel concentrations in peripheral blood (and bone marrow and CSF if available) will be listed, graphed and summarized (arithmetic and geometric means, standard deviation, CV%, CV% geometric mean, minimum, median and maximum) by time points and Month 3 response as assessed by the following:

- Tisagenlecleucel transgene levels as measured by q-PCR
- Tisagenlecleucel transduced cells measured by flow cytometry of CD3-positive/ CD4-positive and CD3-positive/CD8-positive tisagenlecleucel transduced cells if feasible.

The cellular kinetics parameters listed in [Table 8-10](#) along with other relevant cellular kinetics parameters will be estimated, if feasible, from the individual concentration versus time profiles using a non-compartmental approach within the modeling program Phoenix[®] (Pharsight, Mountain View, CA) and reported by best response category. The non-quantifiable

concentrations will be imputed to zero for concentration summaries, and will not be included for estimation of cellular kinetics parameters. Results reported but deemed unreliable will be flagged and excluded from the summaries and cellular kinetics parameter derivations.

Descriptive statistics of cellular kinetics parameters (arithmetic and geometric means, standard deviation, CV%, CV% geometric mean, minimum, median and maximum) will be summarized by Month 3 response for Arm A as well as for patients who crossover and receive tisagenlecleucel. For T_{max} and T_{last} only minimum, median and maximum will be presented.

The relationship between tisagenlecleucel cellular kinetics and dose and response will be explored using appropriate logistic regression and cox regression models if sufficient data is available for Arm A and for patients who crossover and receive tisagenlecleucel. Further details will be provided in the SAP.

12.5.5 Biomarkers

As a project standard, Novartis Oncology Biostatistics and Data Management will analyze only biomarkers collected in the clinical database. Studies are often not adequately powered to assess specific biomarker-related hypotheses, for this reason the exploratory biomarker analyses should be considered as promoting the generation of new scientific hypotheses or observing new trends. These hypotheses may be compared with results found in literature as well as verified with data derived from subsequent clinical trials. No adjustment for multiple comparisons is usually planned for exploratory analyses. Additional post hoc exploratory assessments are expected and may be performed.

Additional analysis may be performed after the completion of the end-of-study CSR and will be documented in separate reports. These analyses may include but are not limited to the meta-analysis of data from this study combined with data from other studies or the analysis of biomarkers generated from samples collected during the study but analyzed after the database lock and completion of the CSR. The data analysis will be described in an addendum of the SAP or in a stand-alone analysis plan document, as appropriate.

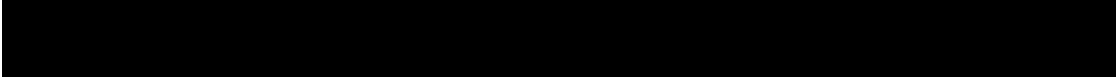
There may be circumstances when a decision is made to stop sample collection, or not perform or discontinue the analysis due to either practical or strategic reasons (e.g. issues related to the quality and/or quantity of the sample or issues related to the assay). Under such circumstances, the number of samples may be inadequate to perform a rigorous data analysis and the available data will only be listed and potentially summarized.

12.5.5.1 Biomarker data analysis set

The Full Analysis Set will be used for all biomarker analysis. Unless otherwise specified, all statistical analyses of biomarker data will be performed on patients with biomarker data.

12.5.5.2 Data handling

Serum cytokine values below the lower limit of quantitation (which may be reported with the label Lower Limit of Quantification [LLOQ]) or have a numerical value below the assay's lower limit of quantification) will be imputed / replaced as $0.5 \times \text{LLOQ}$, which will be specified by the performing lab and is assay and analyte specific. In some cases a value, although below LLOQ, is reported, this value should not be used and the data should be imputed as $0.5 \times \text{LLOQ}$.



12.5.5.3 PD-1, PD-L1 and PD-L2 status and other exhaustion markers

CD19 expression in tumor biopsy specimens at baseline, PD-1 and PD-L1 expression levels and their interaction score if available will be listed and summarized for Arm A and crossover patients. CD19, PD-1, PD-L1 and PD-1/PD-L1 interaction score will also be summarized by clinical response for Arm A and progressive disease patients.

12.5.5.4 Soluble immune factors

The profile of blood soluble proteins and inflammatory cytokines and receptors (IL-10, interferon gamma, IL-6, CRP, and ferritin) will be listed and summarized by patient and time point for Arm A and crossover patients. Baseline and absolute and relative change (percent and or fold change) from baseline will be calculated for each time point and summarized using sample size, mean, standard deviation, median, minimum and maximum. If both the baseline and post baseline values are below Lower Limit of Quantification (LLOQ), absolute, percent and fold change from baseline will not be imputed and reported as missing. Baseline levels may also be summarized by clinical response status and relevant adverse events and potentially graphed using strip plots. In addition, the maximum change from baseline measure for each cytokine may also be graphed against clinical response status and relevant adverse events using strip plots. Patient level and averaged cytokine measures and percent change from baseline may be displayed using longitudinal plots.

12.5.5.5 MRD by Ig deep sequencing

MRD by Ig deep sequencing may be used to identify the dominant tumor clone sequence in blood at baseline and to track clearance or re-appearance of the same clone sequence in subsequent analysis time points. The tumor clonal distribution may be listed for Arm A and crossover patients and percent change from baseline will be summarized if applicable. Patient level absolute and relative changes may be displayed using longitudinal plots. Association between MRD and clinical outcome may be performed.

12.5.5.6 Genomic and/or Next Generation Sequencing (NGS) analysis

Genomic and/or NGS analysis in relation with clinical endpoints will be performed and documented in separate reports.

Potential analysis exploring relationship of efficacy/safety endpoints with tumor cells mutation and/or gene expression could be also conducted. Analysis of leukocyte transcriptome changes pre and post tisagenlecleucel administration and the correlations between apheresis/cell product and clinical responses (efficacy, safety and cellular kinetic parameters) will be summarized in a separate report.

12.5.5.7 B cell and T cell characterization

The levels of blood B and/or T cells will be listed and summarized by patient and time point for all enrolled patients. Absolute number and/or frequencies of total B cell populations will be listed and summarized by patient and time point. Baseline and change from baseline to minimum cell number may also be summarized by response status and potentially graphed using strip plots.



T cell subsets by immunophenotyping within tisagenlecleucel positive and/or tisagenlecleucel negative populations will be explored in relation to safety and efficacy endpoints for Arm A and crossover patients. Data may also be summarized by response status and CRS severity and potentially graphed using strip plots. Patient level and average longitudinal plots of the cell counts and percent changes from baseline may be generated.

12.5.5.8 Molecular characteristics of tisagenlecleucel apheresis product /final product

Apheresis product and/or final product molecular read-outs (e.g. immune cell subsets, T cell differentiation and exhaustion markers, gene expression) will be assessed, listed and summarized by clinical response and/or relevant adverse events for Arm A and crossover patients and summarized in a separate report.

12.5.6 Efficacy in sub-populations

Clinical outcomes (ORR, DOR, EFS and OS) will be summarized descriptively by the following sub-populations:

- Immunogenicity to tisagenlecleucel:
- prevalence of immunogenicity against tisagenlecleucel (pre-existing), both humoral and cellular
- incidence of immunogenicity against tisagenlecleucel, both humoral and cellular
- Double-hit/triple-hit patients with Bcl-2, Bcl-6 and c-myc expression

12.6 Analysis of exploratory endpoints

12.6.1 Efficacy and safety after crossover

The main efficacy and safety endpoints (ORR, OS AE and PRO) will also be summarized after tisagenlecleucel infusion for patients crossed over to tisagenlecleucel arm.

12.6.2 Healthcare resource utilization

Data relating to resource utilization will be used to support health economic evaluations.

Number of tisagenlecleucel inpatients and outpatients infusions will be summarized Descriptive statistics of hospitalizations, including the total and average number and duration of hospitalizations, will be provided by treatment arm.

Details of data analysis will be specified in the analysis plan as appropriate.

12.7 Interim analyses

No interim analysis is planned for this trial for the primary endpoint of EFS. A hierarchical testing procedure will be adopted and the statistical test for OS will be performed only if the primary efficacy endpoint, EFS is statistically significant.

A maximum of two analyses are planned for OS: 1) an interim analysis at the time of the primary analysis for EFS (provided EFS is significant, as outlined in [Section 12.5](#)) in FAS and 2) a final

analysis for OS at approximately 5 years from the first patient randomized. Haybittle–Peto boundary will be used for testing OS.

12.8 Sample size calculation

12.8.1 Primary endpoints

Based on the data from the ORCHARRD study (Novartis unpublished analyses), EFS time for patients who were randomized to receive salvage chemotherapy (DHAP plus Rituximab or DHAP plus Ofatumumab), who never reached CR before or relapsed within 12 months from response to previous therapy, or had a response of PR, SD or PD to previous therapy was considered as a reference for SOC. In ORCHARRD study, for these patients, who continue to be in SD status at the end of cycle 2/3 (which is earlier than the 12 week assessment, each cycle: 21 days) or had progressed earlier than the 12 week assessment, based on the definition of EFS endpoint used in BELINDA (where patients with documented SD/PD at the 12 week assessment (+/-1 week) is considered an EFS event), EFS event time was adjusted to 12 weeks, to account for these earlier events.

The 9 month EFS rate is estimated to be 22.32% in SOC arm and is assumed to be 40% in tisagenlecleucel arm. Due to delayed tisagenlecleucel infusion of 6 weeks and ignoring SD/PD at week 6, we assume piecewise hazard rate in both treatment arms. The hazard ratio between two arms during the first 6 weeks is assumed to be 1 and 0.61 after 6 weeks. Given those assumptions, a total of 200 EFS events are required to have 92% power at an one-sided 2.5% level of significance to reject the null hypothesis (i.e. the survival functions for EFS in the two arms are identical), using a stratified log-rank test with equal weights. The sample size calculation was conducted via simulation with software package East 6.4.

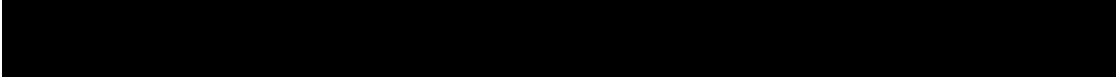
Based on a recruitment period of approximately 21 months using staggered enrollment rates of 2, 10, and 16 patients in the 1st 3 months followed by 17 patients thereafter, and assuming 15% drop-out rate, a total of approximately 318 patients will need to be randomized to the two treatment arms in a 1:1 ratio. Given the above assumptions, it is estimated that the 200th EFS event will be observed at approximately 23 months from the date of first patient randomized.

At least 36 Chinese participants (from China mainland) are envisioned to be randomized in the global study main cohort and China extension cohort to support China registration. The number of participants to be enrolled in the China Extension cohort will depend on the number of Chinese participants in the global study main cohort. The recruitment in the China extension cohort will not start if the number of participants enrolled in the global study main cohort is sufficient to support China registration.

13 Ethical considerations and administrative procedures

13.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented, executed and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US CFR 21), and with the ethical principles laid down in the Declaration of Helsinki.



13.2 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, written informed consent form, consent form updates, participant recruitment procedures (e.g., advertisements) and any other written information to be provided to participants. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

13.3 Publication of study protocol and results

The protocol will be registered in a publicly accessible database such as clinicaltrials.gov and as required in EudraCT. In addition, after study completion (defined as last patient last visit) and finalization of the study report the results of this trial will be submitted for publication and posted in a publicly accessible database of clinical trial results, such as the Novartis clinical trial results website and all required Health Authority websites (e.g. Clinicaltrials.gov, EudraCT etc).

For details on the Novartis publication policy including authorship criteria, please refer to the Novartis publication policy training materials that were provided to you at the trial investigator meetings.

13.4 Quality control and quality assurance

Novartis maintains a robust Quality Management System (QMS) that includes all activities involved in quality assurance and quality control, to ensure compliance with written Standard Operating Procedures as well as applicable global/local GCP regulations and ICH Guidelines.

Audits of investigator sites, vendors, and Novartis systems are performed by auditors, independent from those involved in conducting, monitoring or performing quality control of the clinical trial. The clinical audit process uses a knowledge/risk based approach.

Audits are conducted to assess GCP compliance with global and local regulatory requirements, protocols and internal SOPs, and are performed according to written Novartis processes.

14 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of participants should be administered as deemed necessary on a case by case basis. Under no circumstances including incidental collection is an investigator allowed to collect additional data or conduct any additional procedures for any purpose involving any investigational drugs under the protocol, other than the purpose of the study. If despite this interdiction prohibition, data, information, observation would be incidentally collected, the investigator shall immediately disclose it to

Novartis and not use it for any purpose other than the study, except for the appropriate monitoring on study participants.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC and health authorities, where required, it cannot be implemented.

14.1 Protocol Amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, health authorities where required, and the IRB/IEC prior to implementation.

Only amendments that are required for participant safety may be implemented immediately provided the health authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified.

Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any participant included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations.



15 References (available upon request)

The American Association for the Study of Liver Disease and the Infectious Diseases Society of America – HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C (2014-2017)

A Predictive Model for Aggressive Non-Hodgkin's Lymphoma - The International Non-Hodgkin's Lymphoma Prognostic Factors Project (1993) *N Engl J Med*; 329:987-94.

Al-Hamadani M, Habermann TM, Cerhan JR, et al (2015) Non-Hodgkin lymphoma subtype distribution, geodemographic patterns, and survival in the US: A longitudinal analysis of the National Cancer Data Base from 1998 to 2011. *Am J Hematol*; 90(9):790-5.

Alizadeh AA, Eisen MB, Davis RE, et al (2000) Distinct types of diffuse large B-cell lymphoma identified by gene expression profiling. *Nature*; 403(6769):503-511.

Amos SM, Duong CP, Westwood JA et al (2011) Autoimmunity associated with immunotherapy of cancer. *Blood*; 118(3):499-509.

Anon (2006a) Guidance for industry: gene therapy clinical trials-observing subjects for delayed adverse events; availability. Available from <https://www.federalregister.gov/articles/2006/11/28/E6-20129/guidance-for-industry-gene-therapy-clinical-trials-observing-subjects-for-delayed-adverse-events> (Accessed 13 March 2017).

Anon (2006b) Guidance for industry: supplemental guidance on testing for replication competent retrovirus in retroviral vector based gene therapy products and during follow-up of patients in clinical trials using retroviral vectors. Available from <http://www.fda.gov/biologicsbloodvaccines/guidancecomplianceregulatoryinformation/guidances/cellularandgenetherapy/ucm072961.htm>.

Anon (2009) Guideline on follow-up of patients administered with gene therapy medicinal products. Available from http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/11/WC500013424.pdf.

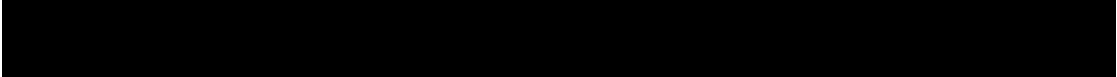
Anon (2020) Guidance for industry: Testing of Retroviral Vector-Based Human Gene Therapy Products for Replication Competent Retrovirus During Product Manufacture and Patient Follow-up. Available from <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/testing-retroviral-vector-based-human-gene-therapy-products-replication-competent-retrovirus-during>.

Averbeck M, Gebhardt C, Emmrich F, et al (2007) Immunologic principles of allergic disease. *J Dtsch Dermatol Ges*; 5(11):1015-28.

Awasthi R, Tam CS, Jaeger U, et al (2017) Clinical Pharmacology of CTL019 in Patients with Relapsed/Refractory (r/r) Diffuse Large B-Cell Lymphoma (DLBCL). *Blood*; 130:5211.

Baetz T, Belch A, Couban S, et al (2003) Gemcitabine, dexamethasone and cisplatin is an active and non-toxic chemotherapy regimen in relapsed or refractory Hodgkin's disease: a phase II study by the National Cancer Institute of Canada Clinical Trials Group. *Ann Oncol*; 14:1762-1767.

- Barrington SF, Mikhaeel NG, Kostakoglu L, et al (2014) Role of imaging in the staging and response assessment of lymphoma: consensus of the international conference on malignant lymphomas imaging working group. *J Clin Oncol*; 32:3048-58.
- Bendamustine full prescribing information. Available from: dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=39d53698-57fa-7c99-fc5b-f52a55684826#section-5.6. Accessed 13Mar2017.
- Biffi A, Montini E, Lorioli L, et al (2013) Lentiviral hematopoietic stem cell gene therapy benefits metachromatic leukodystrophy. *Science*; 341 (6148): 1233158-1- 1233158-11
- Bonifant CL, Jackson HJ, Brentjens RJ, et al (2016) Toxicity and management in CAR T-cell therapy. *Mol Ther Oncolytics*; 3:16011. doi: 10.1038/mto.2016.11. eCollection 2016.
- Brentjens R, Yeh R, Bernal Y, et al (2010) Treatment of chronic lymphocytic leukemia with genetically targeted autologous T cells: case report of an unforeseen adverse event in a phase I clinical trial. *Mol Ther*; 18(4):666-668.
- Calogero A, DeLeij LF, Mulder NH, et al (2000) Recombinant T-cell receptors: an immunologic link to cancer therapy. *J Immunol*; 23(4):393-400.
- Carter GC, Liepa AM, Zimmermann AH, et al (2008) Validation of the Functional Assessment of Cancer Therapy–Lymphoma (FACT-LYM) in Patients with Relapsed/Refractory Mantle Cell Lymphoma. *Blood*; 112:2376.
- Cartier N, Hacein-Bey-Abina S, Bartholomae CC, et al (2009) Hematopoietic stem cell gene therapy with a lentiviral vector in X-linked adrenoleukodystrophy. *Science*; 326(5954): 818-823
- Chang C, Gershwin ME, (2010) Drugs and autoimmunity – A contemporary review and mechanistic approach. *Journal of Autoimmunity*; 34:266-275.
- Chavey WE, Blaum CS, Bleske BE, et al (2001) Guideline for the management of heart failure caused by systolic dysfunction: Part I. Guideline development, etiology and diagnosis. *Am Fam Physician*; 64(5):769-74.
- Cheson BD, Fisher RI, Barrington SF, et al (2014) Recommendations for initial evaluation, staging, and response assessment of Hodgkin and Non-Hodgkin lymphoma: The Lugano Classification. *J Clin Oncol*; 32:3059-3067.
- Cheson BD, Horning SJ, Coiffier B, et al (1999) Report of an international workshop to standardize response criteria for non-Hodgkin's lymphomas. *J Clin Oncol* 17:1244-1253.
- Cheson BD, Pfistner B, Juweid ME, et al (2007) Revised response criteria for malignant lymphoma. *J Clin Oncol* 25:579-586.
- Chiappella A, Castellino A, and Vitolo U (2016) State-of-the-art Therapy for Advanced-stage Diffuse Large B-cell Lymphoma. *Hematol Oncol Clin North Am*; 30(6): 1147–1162.
- Chong EA, Svoboda J, Nasta SD, et al (2016) Chimeric Antigen Receptor Modified T Cells Directed Against CD19 (CTL019) in Patients with Poor Prognosis, Relapsed or Refractory CD19+ Follicular Lymphoma: Prolonged Remissions Relative to Antecedent Therapy. *Blood*; 128:1100
- Clay TM, Morse M, Lyerly HK (2002) Redirecting cytotoxic T lymphocyte responses with T-cell receptor transgenes. *Expert Opin Biol Ther*; 2(4):353-360.

- Coiffier B, Sarkozy C (2016) Diffuse large B-cell lymphoma: R-CHOP failure-what to do? Hematology Am Soc Hematol Educ Program; (1):366-378.
- Corominas M, Gastaminza G, Lobera T (2014) Hypersensitivity reactions to biological drugs. J Investig Allergol Clin Immunol; 24(4):212-25.
- Crump M, Kuruvilla J, Couban S, et al (2014) Randomized Comparison of Gemcitabine, Dexamethasone and Cisplatin Versus Dexamethasone, Cytarabine, and Cisplatin Chemotherapy Before Autologous Stem-Cell Transplantation for Relapsed and Refractory Aggressive Lymphomas: NCIC-CTG LY.12. J Clin Oncol; 32(31):3490-3496.
- Crump M, Neelapu SS, Farooq U et al (2016) Outcomes in refractory aggressive diffuse large b-cell lymphoma (DLBCL): Results from the international SCHOLAR-1 study. Journal of Clinical Oncology 34-Suppl 15:7516.
- Crump M, Neelapu SS, Farooq U, et al (2017) Outcomes in refractory aggressive diffuse large b-cell lymphoma (DLBCL): Results from the international SCHOLAR-1 study. Blood;130(16):1800-1808.
- Cyclophosphamide full prescribing information. Available from: dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=591d9955-3d9c-4cdc-a308-2f1288376b9f. Accessed 13Mar2017.
- Descotes J and Gouraud A (2008) Clinical immunotoxicity of therapeutic proteins. Expert Opin Drug Metab Toxicol; 4(12):1537-49.
- Descotes J (2012) Safety immunopharmacology: evaluation of the adverse potential of pharmaceuticals on the immune system. J Pharmacol Toxicol Methods; 66(2):79-83.
- Dreyling M, Ghielmini M, Rule S, et al (2016) Newly Diagnosed and Relapsed Follicular Lymphoma: ESMO Clinical Practice Guidelines Diagnosis, Treatment, and Follow-up. Ann Oncol; 27Suppl 5: 83-90.
- Dudley M, Wunderlich J, Robbins P, et al (2002) Cancer regression and autoimmunity in patients after clonal repopulation with antitumor lymphocytes. Science; 298:850-854.
- Dudley M, Wunderlich J, Yang J, et al (2005) Adoptive cell transfer therapy following nonmyeloablative but lymphodepleting chemotherapy for the treatment of patients with refractory metastatic melanoma. J Clin Oncol; 23(10):2346-57.
- Dummer W, Niethammer AG, Baccala R, et al (2002) T cell homeostatic proliferation elicits effective antitumor autoimmunity. J Clin Invest; 110(2):185-192.
- Elstrom RL, Martin P, Ostrow K, et al (2010) Response to second-line therapy defines the potential for cure in patients with recurrent diffuse large B-cell lymphoma: implications for the development of novel therapeutic strategies. Clin Lymphoma Myeloma Leuk; 10(3):192-196.
- Eshhar Z, Waks T, Bendavid A, et al (2001) Functional expression of chimeric receptor genes in human T cells. J Immunol Methods; 248:67-76.
- FDA Guideline (2007) Clinical trial endpoints for the approval of cancer drugs and biologics, May 2007. Ferlay J, Soerjomataram I, Dikshit R, et al (2015) Cancer Incidence and Mortality Worldwide: Sources, methods, and major patterns in GLOBOCAN 2012. Int J Cancer; 136:E359-E386.
- 

Finney HM, Akbar AM, Lawson AD (2004) Activation of resting human primary T cells with chimeric receptors: costimulation from CD28, inducible, costimulator, CD134 and CD137 in series with signals from the TCR zeta chain. *J Immunol*; 172:104-113.

Finney HM, Lawson AD, Bebbington CR, et al (1998) Chimeric receptors providing both primary and costimulatory signaling in T cells from a single gene product. *J Immunol*; 161:2791-2797.

Fludarabine full prescribing information. Available from: dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=fb70b8e8-aca8-4d67-8791-063ac4081073. Accessed 13Mar2017.

Friedberg JW (2011) Relapsed/refractory diffuse large B-cell lymphoma. *Hematology Am Soc Hematol Educ Program*; 2011:498-505.

Friedman DL, Whitton J, Leisenring W, et al (2010) Subsequent neoplasms in 5-year survivors of childhood cancer: the Childhood Cancer Survivor Study. *J Natl Cancer Inst*; 102(14):1083-95.

Friedmann-Morvinski D, Bendavid A, Waks T, et al (2005) Redirected primary T cells harboring a chimeric receptor require costimulation for their antigen-specific activation. *Blood*; 105:3087-3093.

Gilbert MJ (2017) Severe Neurotoxicity in the Phase 2 Trial of JCAR015 in Adult B-ALL (ROCKET Study): Analysis of Patient, Protocol and Product Attributes. Society for Immunotherapy of Cancer's (SITC), 32nd Annual Meeting, National Harbor MD, 08-12 – Nov-2017

Gisselbrecht C, Glass B, Mounier N, et al (2010) Salvage regimens with autologous transplantation for relapsed large B-cell lymphoma in the rituximab era. *J Clin Oncol*; 28(27): 4184-4190.

Goldrath AW, Bevan MJ (1999) Selecting and maintaining a diverse T-cell repertoire. *Nature*; 402(6759):255-262.

Gopal AK, Kahl BS, de Vos S, et al (2014) PI3K δ inhibition by idelalisib in patients with relapsed indolent lymphoma. *N Engl J Med*; 370(11):1008-18.

Gross G, Eshhar Z (1992) Endowing T cells with antibody specificity using chimeric T cell receptors. *FASEB J*; 6:3370-3378.

Gross G, Waks T, Eshhar Z (1989) Expression of immunoglobulin-T-cell receptor chimeric molecules as functional receptors with antibody-type specificity. *Proc Natl Acad Sci USA*; 86(24):10024-10028.

Grupp SA, Kalos M, Barrett D, et al (2013) Chimeric antigen receptor-modified T cells for acute lymphoid leukemia. *N Engl J Med*; 368(16):1509-1518.

Hans CP, Weisenburger DD, Greiner TC, et al (2004) Confirmation of the molecular classification of diffuse large B-cell lymphoma by immunohistochemistry using a tissue microarray. *Blood*; 103(1):275-282.

Hombach A, Heuser C, Abken H (2002) The recombinant T cell receptor strategy: insights into structure and function of recombinant immunoreceptors on the way towards an optimal receptor design for cellular immunotherapy. *Curr Gene Ther*; 2:211-226.

- Howlader N, Noone A, Krapcho M (2011) SEER Cancer Statistics Review (CSR) 1975-2015. Available from: http://seer.cancer.gov/csr/1975_2011, Accessed on 14/May/2017.
- Hwang JP, Somerfield MR, Alston-Johnson DE (2018) Hepatitis B Virus Screening for Patients with Cancer Before Therapy: American Society of Clinical Oncology Provisional Clinical Opinion Update. *J Clin Oncol* 33:2212-2220
- Jaffe ES (2009) 2008 WHO classification of lymphomas: implications for clinical practice and translational research. *Hematology Am Soc Hematol Educ Program* :523-31.
- June CH, Blazar BR, Riley JL (2009) Engineering lymphocyte subsets: tools, trials and tribulations. *Nat Rev Immunol*; 9:704-716.
- June CH (2007) Adoptive T cell therapy for cancer in the clinic. *J Clin Invest*; 117(6):1466-1476.
- Kaech SM, Ahmed R (2001) Memory CD8⁺ T cell differentiation: Initial antigen encounter triggers a developmental program in naïve cells. *Nat Immunol*; 2(5):415-422.
- Kantarjian HM, Su Y, Jabbour EJ, et al (2016) Patient-Reported Outcomes From a Global Phase 3 Randomized Controlled Trial of Inotuzumab Ozogamicin Versus Standard of Care Chemotherapy for Relapsed/Refractory Acute Lymphoblastic Leukemia. Presented at American Society of Hematology 58th Annual Meeting and Exposition; December 3–6, 2016, San Diego, CA, USA.
- Kewalramani T, Zelenetz AD, Nimer SD et al (2004) Rituximab and ICE as second-line therapy before autologous stem cell transplantation for relapsed or primary refractory diffuse large B-cell lymphoma. *Blood*; 103:3684-3688.
- Kimura M, Yamaguchi M, Nakamura S et al (2007) Clinicopathologic Significance of Loss of CD19 Expression in Diffuse Large B-Cell Lymphoma, *Int J Hematol*; 85:41-48.
- King C, Ilic A, Koelsch K, et al (2004) Homeostatic Expansion of T Cells during Immune Insufficiency Generates Autoimmunity. *Cell*; 117(2):265-277.
- Klebanoff CA, Khong HT, Antony PA, et al (2005) Sinks, suppressors and antigen presenters: how lymphodepletion enhances T cell-mediated tumor immunotherapy. *Trends Immunol*; 26(2):111-117.
- Kohn DB, Dotti G, Brentjens R (2011) CARs on track in the clinic. *Mol Ther*; 19(3):432-38.
- Krause A, Guo HF, Latouche JB, et al (1998) Antigen-dependent CD28 signaling selectively enhances survival and proliferation in genetically modified activated human primary T lymphocytes. *J Exp Med*; 188(4):619-626.
- Lamers CH, Langeveld SC, Groot-van Ruijven CM, et al (2007) Gene-modified T cells for adoptive immunotherapy of renal cell cancer maintain transgene-specific immune functions in vivo. *Cancer Immunol Immunother*; 56(12):1875-1883.
- Lamers CHJ, Sleijfer S, Vulto AG, et al (2006) Treatment of metastatic renal cell carcinoma with autologous T-lymphocytes genetically retargeted against carbonic anhydrase ix: first clinical experience. *J Clin Oncol*; 24(13):20e-22e.
- Lamers CH, Willemsen R, van Elzakker P, et al (2011) Immune responses to transgene and retroviral vector in patients treated with ex vivo-engineered T cells. *Blood*; 117(1):72-82.

- Lee D, Gardner R, Porter DL, et al (2014) Current concepts in the diagnosis and management of cytokine release syndrome. *Blood*; 124 (2): 188-195.
- Lee DW, Santomasso BD, Locke FL et al (2019) ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells. *Biol Blood Marrow Transplant*; 25(4):625-38.
- Lee L, Wang L, Crump M (2011) Identification of potential surrogate end points in randomized clinical trials of aggressive and indolent non-Hodgkin lymphoma: correlation of complete response, time-to-event and overall survival end points. *Ann Oncol*; 22(6):1392–1403.
- Lenz G, Wright G, Dave SS, et al (2008) Stromal gene signatures in large-B-cell lymphomas. *N Engl J Med*; 359:2313–2323.
- Lenz G, Wright GW, Emre NC, et al (2008) Molecular subtypes of diffuse large B-cell lymphoma arise by distinct genetic pathways. *Proc Natl Acad Sci USA*; 105(36):13520-13525.
- Limsuwan T, Demoly P (2010) Acute symptoms of drug hypersensitivity (urticaria, angioedema, anaphylaxis, anaphylactic shock). *Med Clin North Am*; 94(4):691-710.
- Loubiere LS, Lambert NC, Flinn LJ, et al (2006) Maternal microchimerism in healthy adults in lymphocytes, monocyte/macrophages and NK cells. *Lab Invest*; 86(11):1185–92.
- Maher J, Brentjens R, Gunset G, et al (2002) Human T-lymphocyte cytotoxicity and proliferation directed by a single chimeric TCR zeta/ CD28 receptor. *Nat Biotechnol*; 20:70-75.
- Maude SL, Frey N, Shaw PA, et al (2014) Chimeric antigen receptor T cells for sustained remissions in leukemia. *N Engl J Med*; 371(16):1507-17.
- Maude SL, Laetsch TW, Buechner J, et al (2018) Tisagenlecleucel in Children and Young Adults with B-Cell Lymphoblastic Leukemia. *N. Engl. J. Med.* p. 439-448
- Maus MV, Grupp SA, Porter DL, et al (2014) Antibody-modified T cells: CARs take the front seat for hematologic malignancies. *Blood*, 123, 2625–35.
- Mehta S, Sastry BK, Souza R, et al (2017) Macitentan Improves Health-Related Quality of Life for Patients With Pulmonary Arterial Hypertension: Results From the Randomized Controlled SERAPHIN Trial. *Chest*. 2017 Jan;151(1):106-118.
- Mellman I, Coukos G, Dranoff G (2011) Cancer immunotherapy comes of age. *Nature*; 480(7378):480-9.
- Milone MC, Fish JD, Carpenito C, et al (2009) Chimeric receptors containing CD137 signal transduction domains mediate enhanced survival of T cells and increased antileukemic efficacy in vivo. *Mol Ther*; 17(8):1453-1464.
- Mohanlal R, Qiu Y, Zheng M, et al (2016) Long-Term Safety Follow-Up of Subjects Previously Treated with Non-Replicating Retroviral Vector-Based Gene Therapies. *Mol Diagn Ther*; 20(6):591-602.
- Moller MB, Christensen BE, Pedersen NT (2003) Prognosis of localized diffuse large B-cell lymphoma in younger patients. *Cancer*; 98(3):516-521.

- Mols F, Aaronson NK, Vingerhoets AJ, et al (2007) Quality of life among long-term non-Hodgkin lymphoma survivors: a population-based study. *Cancer* 109(8):1659–1667.
- Montini E, Cesana D, Schmidt M, et al (2006) Hematopoietic stem cell gene transfer in a tumor-prone mouse model uncovers low genotoxicity of lentiviral vector integration. *Nat Biotechnol*; 24(6):687-696
- Moskowitz C, Nimer S, Glassman J, et al (1999) The International Prognostic Index predicts for outcome following autologous stem cell transplantation in patients with relapsed and primary refractory intermediate-grade lymphoma. *Bone Marrow Transplant*; 23(6):561-7.
- Mounier N, El Gnaoui T, Tilly H, et al (2013) Rituximab plus gemcitabine and oxaliplatin in patients with refractory/relapsed diffuse large B-cell lymphoma who are not candidates for high-dose therapy. A phase II lymphoma study association trial. *Haematologica*; 10.3324/haematol.2013.090597.
- Mughal T, Ejaz AA, Foringer JR, et al (2010) An integrated clinical approach for the identification, prevention, and treatment of tumor lysis syndrome. *Cancer Treat Rev*; 36(2):164-76.
- Mullaney BP, Pallavicini MG (2001) Protein-protein interactions in hematology and phage display. *Exp Hematol*; 29(10):1136-1146.
- NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) - B-cell Lymphomas, Guidelines Version 1.2019 (2019).
- Neelapu SS, Tummala S, Kebriaei P, et al (2018) Chimeric antigen receptor T-cell therapy - assessment and management of toxicities. *Nat Rev Clin Oncol*; 15(1):47-62.
- Oerlemans S, Mols F, Nijziel M, et al (2011) The impact of treatment, socio-demographic and clinical characteristics on health-related quality of life among Hodgkin's and non-Hodgkin's lymphoma survivors: a systematic review. *Ann Hematol*; 90:993–1004.
- Palmer DC, Balasubramaniam S, Hanada KI, et al (2004) Vaccine-Stimulated, Adoptively Transferred CD8+ T Cells Traffic Indiscriminately and Ubiquitously while Mediating Specific Tumor Destruction. *J Immunol*; 173(12):7209-7216.
- Park JR, Digiusto DL, Slovak M, et al (2007) Adoptive transfer of chimeric antigen receptor re-directed cytolytic T lymphocyte clones in patients with neuroblastoma. *Mol Ther*; 15:825-833.
- Pérez-De-Lis M, Retamozo S, Flores-Chávez A et al (2017) Autoimmune diseases induced by biological agents. A review of 12,731 cases (BIOGEAS Registry). *Expert Opin Drug Saf*; 16(11):1255-1271
- Pinthus JH, Waks T, Kaufman-Francis K, et al (2003) Immuno-gene therapy of established prostate tumors using chimeric receptor-redirected human lymphocytes. *Cancer Res*; 63:2470-2476.
- Porter DL, Levine BL, Kalos M, et al (2011) Chimeric antigen receptor-modified T cells in chronic lymphoid leukemia. *N Engl J Med*; 365(8):725-733.
- Pule M, Finney H, Lawson A (2003) Artificial T-cell receptors. *Cytotherapy*; 5(3):211-226.
- Ruella M, Xu J, Barrett D, et al (2018) Induction of resistance to chimeric antigen receptor T cell therapy by transduction of a single leukemic B cell. *Nat Med*; 24: 1499-1503

- Sadelain M, Riviere I, Brentjens R (2003) Targeting tumours with genetically enhanced T lymphocytes. *Nat Rev Cancer*; 3:35-45.
- Sant M, Allemani C, Tereanu C (2010) Incidence of hematologic malignancies in Europe by morphologic subtype: results of the HAEMACARE project. *Blood*; 116(19):3724-3734.
- Sarkozy C, Coiffier B (2015) Primary refractory diffuse large B cell lymphoma in the rituximab era. *Curr Opin Oncol*; 27:377-383.
- Schambach A, Zychlinski D, Ehrnstroem B, et al (2013) Biosafety features of lentiviral vectors. *Hum Gene Ther*; 24(2):132-142
- Schuster SJ, Bishop MR, Tam CS, et al (2017) Primary Analysis of Juliet: A Global, Pivotal, Phase 2 Trial of CTL019 in Adult Patients with Relapsed or Refractory Diffuse Large B-Cell Lymphoma. Oral presented at ASH 2017; Atlanta.
- Schuster SJ, Svoboda J, Chong EA, et al (2017) Chimeric Antigen Receptor T Cells in Refractory B-Cell Lymphomas. *N Engl J Med*; 377:2545-2554.
- Sehn LH, Chua N, Mayer J, et al (2016) Obinutuzumab plus bendamustine versus bendamustine monotherapy in patients with rituximab-refractory indolent non-Hodgkin Lymphoma (GADOLIN): a randomised, controlled, open-label, multicentre, phase 3 trial. *Lancet Oncol*; 17(8):1081-93.
- Sehn LH, Goy A, Offner FC, et al (2015) Randomized Phase II Trial Comparing Obinutuzumab (GA101) With Rituximab in Patients With Relapsed CD20+ Indolent B-Cell Non-Hodgkin Lymphoma: Final Analysis of the GAUSS Study. *J Clin Oncol*; 33(30):3467-74.
- Shi Q, Schmitz N, Flowers C, et al (2016) Evaluation of Progression-Free Survival (PFS) As a Surrogate Endpoint for Overall Survival (OS) in First-Line Therapy for Diffuse Large B-Cell Lymphoma (DLBCL): Findings from the Surrogate Endpoint in Aggressive Lymphoma (SEAL) Analysis of Individual Patient Data from 7507 Patients. *Blood*; 128:4196 A.
- Siegel RL, Miller KD, Jemal A (2017) Cancer statistics, 2017. *CA Cancer J Clin*; 67(1):7-30.
- Stevens AM (2016)] Maternal microchimerism in health and disease. *Best Pract Res Clin Obstet Gynaecol*;31:121-30.
- Surh CD, Sprent J (2000) Homeostatic T cell proliferation: how far can T cells be activated to self-ligands? *J Exp Med*; 192(4):F9-F14.
- Swerdlow SH, Campo E, Pileri SA, et al (2016) The 2016 revision of the World Health Organization classification of lymphoid neoplasms. *Blood*; 127(20):2375-90.
- Swigris JJ, Brown KK, Behr J, et al (2010) The SF-36 and SGRQ: Validity and first look at minimum important differences in IPF. *Respir Med* 104: 296-304.
- Teachey DT, Bishop MR, Maloney DG, et al (2018) Toxicity Management after chimeric antigen receptor T cell therapy: one size does not fit 'ALL'. *Nat Rev Clin Oncol* 15: 218.
- Tey SK (2014) Adoptive T-cell therapy: adverse events and safety switches. *Clin Transl Immunology*; 3(6):e17.
- Tilly H, Gomes da Silva M, Vitolo U, et al (2015) Diffuse large B-cell lymphoma (DLBCL): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up: on behalf of the ESMO Guidelines Committee. *Ann Oncol*; 26(Suppl 5):v116–v125.

Turtle CJ, Hanafi LA, Berger C, et al (2016) 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* p. 355ra116.

Van den Neste E, Schmitz N, Mounier N, et al (2016) Outcome of patients with relapsed diffuse large B-cell lymphoma who fail second-line salvage regimens in the International CORAL study. *Bone Marrow Transplantation*; 51:51–57.

Van den Neste E, Schmitz N, Mounier N, et al (2017) Outcomes of diffuse large B-cell lymphoma patients relapsing after autologous stem cell transplantation: an analysis of patients included in the CORAL study. *Bone Marrow Transplantation*; 52: 216–221.

Van Imhoff GW, McMillan A, Matasar MJ, et al (2017) Ofatumumab Versus Rituximab Salvage Chemoimmunotherapy in Relapsed or Refractory Diffuse Large B-Cell Lymphoma: The ORCHARRD Study. *J Clin Oncol*; 35(5): 544-551.

Van Stipdonk MJ, Lemmens EE, Schoenberger SP (2001) Naïve CTLs require a single brief period of antigenic stimulation for clonal expansion and differentiation. *Nat Immunol*; 2(5):423-429.

Velasquez WS, Cabanillas F, Salvador P, et al (1998) Effective salvage therapy for lymphoma with cisplatin in combination with high-dose Ara-C and dexamethasone (DHAP). *Blood*; 71:117–122.

Ware JE, Sherbourne CD (1992) The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care*; 30(6):473-483.

Webster K, Cella D, Yost K (2003) The Functional Assessment of Chronic Illness Therapy (FACIT) Measurement System: properties, applications, and interpretation. *Health and Qual Life Outcomes*. 1; 79.

Zaiss AK, Son S, Chang LJ (2002) RNA 3' readthrough of oncoretrovirus and lentivirus: implications for vector safety and efficacy. *J Virol*; 76(14):7209-7219

Zhou Z, Sehn LH, Rademaker AW, et al (2014) An enhanced International Prognostic Index (NCCN-IPI) for patients with diffuse large B-cell lymphoma treated in the rituximab era. *Blood*; 123(6):837-42.

16 Appendices

16.1 Appendix 1: Assessment algorithms for hepatitis B and C status at screening

Hepatitis B

1. Test for HBsAg, HBcAb, HBsAb.
2. If all these three tests are negative, the patient is eligible.
3. If HBsAb only is positive
 - a. the patient is eligible in absence of signs of hepatitis (e.g. increase of ALT/AST)
 - b. test for HBV DNA, in presence of signs of hepatitis (e.g. increase of ALT/AST)
4. If HBsAg is positive, the patient is NOT eligible.
5. If HBsAg is negative but either HBcAb or both HBcAb and HBsAb are positive, test for HBV DNA.
 - a. If HBV DNA is positive, the patient is **NOT** eligible.
 - b. If HBV DNA is negative, the patient is eligible

Hepatitis C

1. Test for HCV Ab
2. If HCV Ab is negative, the patient is eligible.
3. If HCV Ab is positive, test for HCV RNA.
 - a. If HCV RNA is negative, the patient is eligible.
 - b. If HCV RNA is positive, the patient is **NOT** eligible.

Patients with a history of hepatitis B or C should be managed according to the current guidance by American Society of Clinical Oncology ([Hwang et al, 2018](#)) and HCV Guidance from the [American Association for the Study of Liver Disease-Infectious Disease Society of America guidelines \(2014-2017\)](#)

16.2 Appendix 2: Guidelines for efficacy evaluation in non-Hodgkin-Lymphoma studies

16.2.1 Introduction

The purpose of this document is to provide working definitions and rules to evaluate efficacy in non-Hodgkin lymphoma (NHL) studies conducted by Novartis. This document is based on the International Working Group response criteria ([Cheson et al 1999](#)), the International Harmonization Project revised response criteria ([Cheson et al 2007](#)), and the revised Consensus of the International Conference on Malignant Imaging Working Group and the Lugano Classification ([Barrington et al 2014](#); [Cheson et al 2014](#)), and it is intended for studies of radiographically measurable disease. For studies without measurable disease, e.g., studies of consolidation of complete response, maintenance treatment, or autologous stem cell transplantation, see [Appendix A](#).

16.2.2 Methodologies

16.2.2.1 Computed tomography (CT)

The same method of assessment and technique should be used to characterize each identified and reported lesion throughout the study. Contrast-enhanced CT of neck, chest, abdomen and pelvis, from skull base through lesser trochanters ensuring complete coverage of the pelvis and inguinal areas, should be performed using a ≤ 5 mm slice thickness with a contiguous reconstruction algorithm. If a patient has a CT contrast allergy or develops it during the trial, non-contrast CT of the chest plus contrast-enhanced MRI of abdomen and pelvis are acceptable for a follow up. Chest MRI is not recommended due to respiratory artifacts.

16.2.2.2 Positron emission tomography (PET)

Studies of FDG-avid histologies require PET using the radiotracer ^{18}F -fluorodeoxyglucose (FDG) to confirm any new CR determined by CT. PET will not be required to confirm progression or relapse.

PET scans should cover the whole body from base of skull to mid-thigh. Examinations should be consistent across all time points including amount of tracer, location of injection, arm location, and scan delay. Information of height, weight, gender, administered dose, time between dose administration and imaging, and glucose level are required for each time point. PET images should be converted to standardized uptake value (SUV) maps to support comparison across time points and to standardize viewing conditions.

16.2.2.3 PET-CT

Hybrid PET-CT may be used to acquire PET and CT images if CT images produced by the scanner are of diagnostic quality and include intravenous contrast. Non-diagnostic CT images acquired for attenuation purposes during PET-CT are NOT acceptable as the only images for the time point.

If diagnostic CT and PET are to be acquired on the same day, PET must be performed prior to CT with IV contrast to avoid compromising PET results.

Thus, any of the three following imaging methodologies are possible in a lymphoma study:

- PET-CT with diagnostic CT
- PET-CT with non-diagnostic CT and dedicated diagnostic CT
- Dedicated diagnostic CT and dedicated FDG PET

16.2.2.4 Magnetic resonance imaging (MRI) and PET-MRI

MRI or PET-MRI is an acceptable method of imaging if CT is contraindicated e.g., due to CT contrast allergy. If at baseline a patient is known to be allergic to CT contrast or develops allergy during the trial, the following change in imaging modality will be accepted for follow up: a non-contrast CT of the chest plus contrast-enhanced MRI of abdomen and pelvis (MRI of the chest is not recommended due to respiratory artifacts).

16.2.2.5 Five point scale (5PS)

To standardize PET interpretation, a simple reproducible scoring method called the five point scale (5PS) or the Deauville criteria has been implemented for initial staging and assessment of interim and end of treatment responses ([Barrington et al 2014](#)). The 5PS assesses the most intense uptake in a site of disease ([Table 16-1](#)).

Table 16-1 Five Point Scale (5PS)

Score	Findings
Score 1	No uptake above background
Score 2	Uptake \leq mediastinum
Score 3*	Uptake > mediastinum, but \leq liver
Score 4**	Uptake moderately > liver
Score 5**	Uptake markedly higher than liver and/or new lesions

* The protocol will need to define the significance of a score 3, depending on the studied disease, patient characteristics and goal of therapy.

- Score 3 will be considered PET negative unless otherwise specified in the protocol (e.g. de-escalation studies, in which case CMR will be based on 5PS of 1 or 2 only, and PMR/NMR/PMD will be based on 5PS of 3,4 or 5)

** Score 4 should be applied to uptake greater than the maximum standard uptake value (SUV) in a large region \ of normal liver and score 5 to uptake 2 times greater than the maximum SUV in the liver. PET images should be converted to SUV maps to support comparison across time points and to standardize viewing conditions.

(New) areas of uptake unlikely to be related to lymphoma will be marked as "X" ([Barrington et al. 2014](#)).

16.2.3 Definitions

16.2.3.1 Disease stage

Extent and involvement by lymphoma is described by the disease stage and is an important prognostic factor. Stage can also influence treatment decisions.

16.2.3.2 Baseline

Baseline examination should be as close as possible to the randomization/start of treatment (e.g., within 4 weeks prior to randomization/start of treatment). Longer periods may be allowed depending on the disease studied and the study design.

16.2.3.3 Nodal vs. extranodal lesion

A lesion can be categorized as:

- Nodal lesion (a lymph node or a nodal mass)
- Extranodal lesion (a lesion located in other organs, including spleen and liver)

16.2.3.4 Measurable disease

All anatomic measurements should be taken in two perpendicular dimensions and recorded in metric notation, using a ruler or calipers.

Throughout this document, a lesion will be called measurable if:

- It can be measured accurately in two perpendicular dimensions: longest diameter (LDi) (also known as transverse diameter), and shortest diameter (SDi), which is the longest diameter perpendicular to LDi (also known as perpendicular diameter). The LDi and SDi must be measured on the same slice.
- For a nodal lesion, LDi is greater than 15 mm, regardless of SDi
- For an extranodal lesion, if both LDi and SDi are greater than 10 mm

A lymph node not meeting the measurability criteria but with LDi greater than 15 mm (e.g. SDi cannot be measured accurately) will constitute a non-measurable nodal lesion if FDG-avid (for FDG-avid histologies).

A lymph node not meeting the measurability criteria but with LDi ranging from 11 mm to 15 mm and with SDi greater than 10 mm will be checked for relationship to disease as follows:

- If it is related to lymphoma, it will constitute a non-measurable nodal lesion (referred to as “involved node” in [Cheson et al \(2007\)](#))
- If not related to lymphoma and not FDG-avid, it will constitute an abnormal lymph node but not a nodal lesion for FDG-avid histologies

All lesions visible on PET but not on CT/MRI will be treated as non-measurable.

Bulky disease

Bulky disease is captured by means of the longest measurement by CT scan. The definition of bulky disease (a minimum size) should be included in the study protocol.

16.2.3.5 Assessable disease

Assessable disease refers to disease presentations that are consistent with lymphoma but are not suitable for measurement, e.g., pleural effusion, ascites, etc. Assessable disease will be followed qualitatively.

16.2.3.6 Index lesion

- Up to 6 of the largest nodes, nodal masses or other lymphomatous lesions, including extranodal lesions, measurable in two diameters (LDi and SDi)
- Should represent overall disease burden and include mediastinal and retroperitoneal disease, if involved

16.2.3.7 Non-index lesion

- All other lesions which are not selected as index lesions but are consistent with lymphoma
- Abnormal nodes and extranodal lesions, both measurable and non-measurable, such as cutaneous, gastrointestinal, and bone lesions, pleural or pericardial effusions, and ascites

16.2.3.8 New lesions

- Regrowth of previously resolved lesions
- A new nodal lesion > 15 mm in any axis
- A new extranodal lesion > 10 mm in any axis
- A new extranodal lesion ≤ 10 mm in any axis that is unequivocal and attributable to lymphoma
- A new assessable lesion attributable to lymphoma (e.g., ascites, pleural effusion)

16.2.4 Efficacy assessments

16.2.4.1 Eligibility

In general, patients should have at least one measurable nodal lesion (greater than 15 mm in the long axis) or at least one measurable extranodal lesion (with both LDi and SDi greater than 10 mm).

16.2.4.2 Methods of disease assessment

16.2.4.2.1 PET combined with diagnostic CT

The integration of PET into more frequently acquired CT evaluation does present a challenge to the way response is assessed in a clinical trial. The study protocol must clearly define the imaging intervals and imaging methods to be used at each imaging visit. PET scans should be performed at pre-specified times for example at randomization before treatment and at clearly defined times during and/or after the end of treatment. PET may also be acquired to confirm CT results.

The same CT imaging modality should be used at baseline and all post-baseline assessments in order to reduce the risk of false responses or progressions based on measurement error. A change in modality can be either a change in contrast use (i.e., with contrast versus without contrast) or a change in technique (e.g. from CT to MRI). Response assessments made after a change in imaging modality should be queried, and if the investigator or blinded central reviewer can provide sufficient justification, then the response can be accepted.

In order to calculate the sum of the product of the perpendicular diameters (PPD) of all index lesions, their size must be recorded throughout the study. Actual lesion measurements should

be entered on the corresponding CRFs. If, during the course of the study, either of the perpendicular diameters of a lesion cannot be reliably measured because of its small size, it is recommended to enter the minimum limit of detection as the diameter size (e.g., 5 mm for spiral CT). In other cases when, during the course of the study, the diameter cannot be reliably measured for reasons other than its size (i.e., borders of the lesion are confounded by neighboring anatomical structures), no measurement should be entered and the lesion cannot be evaluated.

If lesions become confluent over time, it is recommended to measure them as one lesion, report the overall diameters to one of the lesions and assign 0 mm × 0 mm to each of the other previously measured lesions. The PPD of the current confluent mass should be used to measure response, with more than 50% increase in the PPD of the confluent mass compared with nadir of the sum of individual nodes necessary to indicate progressive disease.

If a lesion splits into several discrete lesions, the individual product of the perpendicular diameters (PPDs) of each lesion should be summed together to represent the PPD of the split lesion; this PPD is added to the sum of the PPDs of the remaining lesions to measure response. If subsequent growth of any or all of these discrete nodes occurs, the nadir of each individual node is used to determine progression (as if each individual node was selected as an index lesion at baseline).

16.2.4.2.2 Bone marrow assessment

Bone marrow should be evaluated by biopsy or aspirate in all patients at baseline. If lymphoma involvement in bone marrow is observed at baseline, then biopsy or aspirate should be performed post-baseline to confirm radiological CR. Any deviation from this approach should be justified in the study protocol.

16.2.4.2.3 Physical examination

Skin lesions must be histologically confirmed for lymphoma involvement (the investigational site must document the histological confirmation (yes or no) on the corresponding CRF) and photographed including a ruler (color photography using digital camera). Response assessment of skin lesions will be performed and results will be recorded on the corresponding CRF at baseline and at the time of each radiological assessment.

16.2.4.3 Documentation of disease

For the evaluation of disease at baseline and throughout the study, the following will be recorded.

16.2.4.3.1 FGD uptake

FDG uptake in a nodal or extranodal site that is suggestive of lymphoma will be assessed using SPS.

16.2.4.3.2 Index lesions

A minimum of one measurable index lesion and a maximum of six of the largest dominant nodal and extranodal lesions must be documented at baseline and assessed throughout the study

in two dimensions. The lesions should come from different body regions representative of the patient's overall disease burden and should include mediastinal and retroperitoneal disease, if involved. Two perpendicular dimensions (LDi, SDi) must be recorded on the corresponding CRF at each assessment of a measurable lesion selected to be an index lesion.

Index nodal lesions

Index nodal lesions are selected from the measurable nodal lesions and should be documented at baseline and assessed throughout the study. Index nodal lesions should be from disparate regions of the body including mediastinal and retroperitoneal areas of disease whenever these sites are involved.

Index extranodal lesions

Other organs such as breast and lung can be occasionally involved by lymphoma. Such extranodal lesions (e.g. hepatic nodules) may be included (if measurable) in the six index lesions to be assessed throughout the study. In some cases histological examination may be necessary to confirm that these lesions represent lymphoma involvement (e.g. skin lesions).

16.2.4.3.3 Non-index lesions

Non-index nodal lesions

Nodal lesions not selected as index lesions (both measurable and non-measurable) are considered as non-index lesions. Non-index lesions should be documented at baseline and assessed throughout the study. Measurements of these lesions are not required to be documented on the CRF.

Non-index extranodal lesions

Measurable extranodal lesions not selected as index lesions and all non-measurable extranodal lesions (including non-measurable but assessable disease e.g. pleural effusion) will be documented at baseline and assessed throughout the study as non-index lesions. Measurements of these lesions are not required to be documented on the CRF.

16.2.4.3.4 Spleen involvement

Splenic involvement is determined by imaging: vertical (cranial to caudal) length > 13 cm is considered as involved, and spleen length must be assessed at each imaging time point. Intrasplenic lesions should be followed as index, non-index and new extranodal lesions.

16.2.4.3.5 Liver involvement

Given variability in physical habitus and the impact of numerous medical conditions, assessment of liver size is not considered a reliable measure of hepatic involvement and therefore liver assessment is not included in the Lugano 2014 classification. Intrahepatic lesions should be followed as index, non-index and new extranodal lesions.

16.2.4.3.6 Bone marrow involvement

Lymphoma involvement in bone marrow should be documented in the CRF as "Yes" or "No" at each bone marrow biopsy and/or aspiration.

16.2.4.4 Response evaluation

The efficacy variables in the statistical analysis are based on **overall disease response**, which is a combined evaluation of response based on both radiological and clinical findings, and is determined at each post-baseline assessment. The radiological response is first obtained from CT and PET studies according to the Lugano criteria ([Table 16-1](#)) and overall disease response is then determined by taking into account results of bone marrow biopsies and other clinical information ([Table 16-2](#)).

16.2.4.4.1 Radiological response

There are three separate components to radiological response, all of which should be collected on the CRF at each post-baseline assessment:

1. **CT response** based on anatomical measurements of index/non-index/new lesions and spleen length. The possible response outcomes are complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD) as defined in [Table 16-2](#).
2. **PET response** based on 5PS, changes in intensity or extent of standard uptake values (SUVs) and bone marrow assessments directly from the PET scan. The possible outcomes for PET response are complete metabolic response (CMR), partial metabolic response (PMR), no metabolic response (NMR), or progressive metabolic disease (PMD) as defined in [Table 16-2](#).
3. **Overall radiological response** combines CT response with PET response. The outcomes include CR, PR, SD, and PD. For time points when both CT and PET are available, PET response overrules CT response. Overall radiological response at a time point with CT only may also be affected by PET response obtained at a different time point.

Example

A CT response of PR at the same assessment as a PET response of CMR will constitute an overall radiological response of CR, and (i) a subsequent time point with CT only and CT response of PR will still constitute an overall radiological response of CR, (ii) a previous time point with CT only and CT response of PR may be upgraded to CR at the discretion of the investigator or blinded central reviewer.

Table 16-2 Radiological response assessment

		PET-based response	CT-based response
		Complete Metabolic Response (CMR) (All of the following)	Complete Response (CR) (All of the following)
Complete Response	Index	5PS [†] of 1, 2, or 3* with or without residual mass on 5PS	Nodal lesion: ≤ 15 mm in LDi
	Non-index		Extranodal lesion: Absent (0 mm x 0 mm)
	Spleen		Absent
	New lesions	None	Return to normal (≤ 13 cm)
	Bone marrow	No FDG-avid disease	None
		Partial Metabolic Response (PMR) (all of the following)	Partial Response (PR) (all of the following)

		PET-based response	CT-based response
Partial Response	Index	5PS of 4 or 5 with reduced uptake compared to baseline with respect to SUV intensity or extent. This may apply to the specific hot spot and/ or overall the subject. It is expected that there will be residual mass(es) present.	≥ 50% decrease from baseline in SPD across all index lesions
	Non-index		No increase
	Spleen		≥ 50% decrease from baseline in enlarged portion of spleen <i>Example: If 16 cm, then enlarged portion is 3 cm. A decrease by 2 cm gives a 66.6% decrease</i>
	New lesions	None	None
	Bone marrow	<ul style="list-style-type: none"> Residual uptake higher than uptake in normal marrow but reduced compared with baseline Persistent focal changes in the marrow with nodal response 	Not applicable
		No Metabolic Response (NMR) (all of the following)	Stable Disease (SD) (all of the following)
Stable Disease	Index	5PS of 4 or 5 with no significant change in FDG uptake from baseline	<ul style="list-style-type: none"> <50% decrease from baseline in SPD across all index lesions No criteria for PD are met
	Non-index		No progression
	Spleen		No progression
	New lesions	None	None
	Bone marrow	No change in FDG uptake from baseline	Not applicable
		Progressive Metabolic Disease (PMD) (At least one of the following)	Progressive Disease (PD) (At least one of the following)
Progressive Disease	Index	5PS of 4 or 5 with increased uptake compared to the visually determined nadir with respect to SUV intensity or extent. This may apply to the specific hot spot and/ or overall the subject. and/or <ul style="list-style-type: none"> New FDG-avid foci consistent with lymphoma Consider biopsy or interval scan if etiology of new lesions uncertain 	PPD Progression[#]: An individual node/lesion must be abnormal with: <ul style="list-style-type: none"> LDi > 15 mm AND Increase by ≥ 50% from PPD nadir AND An increase in LDi or SDi from nadir: <ul style="list-style-type: none"> ≥ 5 mm for lesions with LDi ≤ 20 mm at current assessment ≥ 10 mm for lesions with LDi > 20 mm at current assessment
	Non-index		Unequivocal Progression

		PET-based response	CT-based response
	Spleen		<ul style="list-style-type: none"> Progression (increase from baseline by >50% in enlarged portion). Example: If 15 cm at baseline then enlarged portion is 2 cm and an increase by >1 cm would be progression New splenomegaly (> 13 cm and increase by > 2 cm from normal at baseline) Recurrent splenomegaly (normalization followed by increase by > 2 cm from nadir reaching > 13 cm)
	New lesions		<ul style="list-style-type: none"> Regrowth of previously resolved lesions New node > 15 mm in any axis New extranodal site > 10 mm in any axis New extranodal site ≤ 10 mm in LDi, unequivocal and attributable to lymphoma Assessable disease of any size Unequivocally attributable to Lymphoma
	Bone marrow	New/recurrent FDG-avid foci	Not applicable
<p>Abbreviations: LDi Longest diameter; SDi Shortest diameter; PPD Product of perpendicular diameters; SPD Sum of the product of the perpendicular diameters.</p> <p>* Score 3 will be considered PET negative unless otherwise specified in the protocol (e.g. de-escalation studies, in which case CMR will be based on 5PS of 1 or 2 only, and PMR/NMR/PMD will be based on 5PS of 3, 4 or 5)</p> <p># In the context of an agent associated with a flare reaction, caution must be exercised not to confuse the possible tumor flare with progressive disease. It is recommended that either a biopsy be performed or the lesion be reassessed in at least 2 weeks, and if there is continued evidence of tumor progression, the date of progressive disease is the previous evaluation.</p> <p>† PET 5PS 1: no uptake > background; 2: uptake ≤ mediastinum; 3: uptake > mediastinum but ≤ liver; 4: uptake moderately > liver; 5: uptake markedly > liver and/or new lesions; X: new areas of uptake unlikely to be related to lymphoma.</p>			

16.2.4.4.2 Overall disease response

Overall disease response is determined by assessing whether the combined radiological responses at each time point are appropriate, based on bone marrow biopsies and other clinical findings that may be available, such as cytology results, physical examination results of palpable lesions or skin lesions, and biopsies of lymph nodes or extra-nodal lesions (Table 16-3). The possible outcomes for overall disease response are CR, PR, SD, and PD.

For example, suppose there was lymphoma involvement in the baseline bone marrow biopsy, and the month 3 combined radiological response was CR (implying that PET-based bone marrow involvement at month 3 was negative). In that case, overall disease response could only be CR if there was a negative bone marrow biopsy otherwise overall disease response would be downgraded to PR. This is a case where the bone marrow biopsy results overrule the bone

marrow findings on PET. Another example is when the combined radiological response is SD, but cytology results of a pleural effusion show lymphoma involvement: this could lead to an overall disease response of PD.

Overall disease response at each post-baseline assessment should be captured on the CRF, along with the date of response. In addition, the source of any clinical data that affected the overall disease response should be documented.

Table 16-3 Overall disease response

Overall radiological response	Bone marrow biopsy/aspirate	Clinical findings	Overall disease response
CR/PR/SD	Negative at baseline or negative \pm 28 days from assessment	Any except new or recurrent lymphoma involvement	CR/PR/SD
CR	Positive at baseline and either positive (without new or recurrent involvement) or not done \pm 28 days from assessment	Any except new or recurrent lymphoma involvement	PR
PR/SD	Positive at baseline and either positive (without new or recurrent involvement) or not done \pm 28 days from assessment	Any except new or recurrent lymphoma involvement	PR/SD
PD	Any	Any	PD
Any	New or recurrent involvement	Any	PD
Any	Any	New or recurrent lymphoma involvement	PD

16.2.4.5 Efficacy analysis definitions

16.2.4.5.1 Best overall response

The best overall response (BOR) is the best overall disease response recorded from randomization/start of treatment until progressive disease or start of new anticancer therapy, whichever comes first. The definition of new anticancer therapy may need to be defined in the study protocol (e.g., high-dose chemotherapy with autologous stem cell transplantation).

A patient will have a best overall response of CR if they have CR as overall disease response for at least one of the assessments.

A patient will have a best overall response of PR if at least one overall disease response of PR is available (and the patient does not qualify for CR).

A best overall response of SD will be declared when at least one overall disease response of SD is available at least 6 weeks after randomization/start of treatment (and the patient does not qualify for CR or PR). If SD is observed before this minimum follow-up period, and the patient does not qualify for CR, PR or PD, then the best overall response would be unknown (UNK).

If a different minimum follow-up period for SD is more appropriate (e.g., if first post-baseline visit is at 28 days) then this must be specified in the Study Protocol.

A patient will have a best overall response of PD if overall disease response is PD between randomization/start of treatment and the second scheduled post-baseline assessment (and the patient does not qualify for CR, PR or SD).

For example, assuming 12 weeks between assessments and a permitted variation in visit timing of ± 1 week, this would mean during the first 25 weeks after randomization/start of treatment. If PD is observed after this maximum follow-up period, and the patient does not qualify for CR, PR or SD, then the best overall response would be UNK. If a different maximum follow-up period for PD is more appropriate then this must be specified in the Study Protocol.

A patient will have a best overall response of UNK if the patient does not qualify for CR, PR, SD or PD.

Overall disease response at a given assessment may be provided from different sources:

- Per Investigator: overall disease response based on local radiological assessments, using investigator choice of index lesions, measurements and assessments of lesion status and 5PS along with clinical findings
- Per Central Blinded Review, with or without blinded adjudication: based on central review of local radiological assessments, using central reviewer choice of index lesions, measurements and assessments of lesion status and 5PS, along with clinical findings

In studies that include a central blinded review, the Study Protocol should state which source will be used for the primary analysis.

Best overall response is summarized by calculating the **overall response rate (ORR)**, which is defined as the proportion of patients with a best overall response of CR or PR.

Similarly, the complete response rate is the proportion of patients with a best overall response of CR.

16.2.4.5.2 Time to event variables

Most of the time to event variables are defined in this section according to the revised International Working Group response criteria ([Cheson et al 2007](#)). Further details on dates and censoring rules are provided respectively in [Section 16.2.4.5.3](#) and [Section 16.2.4.5.4](#).

Overall survival

Overall survival (OS) is defined as the time from the date of randomization/start of treatment to the date of death due to any cause. If a patient is not known to have died, OS will be censored at the date of last contact.

Progression-free survival

Progression-free survival (PFS) is defined as the time from the date of randomization/start of treatment to the date of event defined as the first documented progression (overall disease response = PD) or death due to any cause. If a patient has not had an event, PFS is censored at the date of the last adequate assessment as defined in [Section 16.2.4.5.3](#).

Time to progression

Time to progression (TTP) is defined as the time from the date of randomization/start of treatment to the date of first documented progression (overall disease response = PD) or death due to lymphoma. If a patient has not had an event, TTP is censored at the date of the last adequate assessment.

Duration of response

Duration of response (DOR) applies only to patients with best overall disease response of CR or PR. It is defined as the time from the date of the first documented overall disease response of CR or PR to the date of first documented progression or death due to lymphoma. If a patient has not had an event, DOR is censored at the date of the last adequate assessment. It should be stated that this analysis might introduce a bias as it includes only responders.

Duration of complete response applies only to patients with best overall disease response of CR. It is defined as the time from the date of the first documented overall disease response of CR to the date of first documented progression or death due to lymphoma. If a patient has not had an event, duration of CR is censored at the date of the last adequate assessment. Duration of CR might be calculated in addition for studies in which a reasonable number of complete responders are seen.

The analysis of DOR should only be used as a descriptive analysis. If used as an inferential comparison between treatments, clear justification must be given in the study protocol.

Time to response

Time to response (TTR) is defined as the time from the date of randomization/start of treatment to the date of first documented overall disease response of PR or CR. Depending on the study design, this analysis could be based on all patients only, or on responders only, or both of these analysis populations may be used. The choice of analysis population for TTR should be stated in the study protocol.

For analysis using all patients, TTR will be censored for patients who did not achieve a PR or CR:

- At maximum follow-up (i.e. FPFV to LPLV used for the analysis) for patients who had a PFS event (i.e. either progressed or died due to any cause)
- At the date of the last adequate assessment otherwise

Time to complete response (TTCR) is defined similarly to TTR except using CR only instead of either PR or CR, and with this difference, the above rules and definitions for TTR also apply to TTCR.

Lymphoma specific survival

Lymphoma specific survival (LSS) is defined as the time from the date of randomization/start of treatment to the date of death documented as a result of lymphoma. If a patient has not had an event, LSS will be censored:

- at the date of last contact if the patient is not known to have died
- at the date of death if the patient died for reason other than lymphoma

Event-free survival

Event-free survival (EFS) may be appropriate in studies of advanced disease where early discontinuation is typically related to intolerance of the study drug. In some protocols, EFS may be considered as a sensitivity analysis for TTP. If a patient has not had an event, EFS is censored at the date of the last adequate assessment as defined in [Section 16.2.4.5.3](#). The definition of event needs to be defined in the Study Protocol according to study design.

16.2.4.5.3 Definition of start and end dates for time to event variables

Assessment date

For each assessment, the assessment date is calculated as:

- the latest date of all radiological measurements (e.g. PET-CT, CT, or MRI), excluding bone marrow biopsy, if overall disease response at that assessment is CR/PR/SD/UNK
- the earliest date of all measurements (e.g. PET-CT, CT, or MRI), including bone marrow biopsy if overall disease response at that assessment is PD

Start date

For all “time to event” variables other than the duration of response variables, the date of randomization/start of treatment will be used as the start date.

For the calculation of duration of response variables the following start date should be used:

- Date of first documented response is the assessment date of the first overall disease response of CR for duration of complete response or CR/PR for duration of response

End date

The end dates which are used to calculate ‘time to event’ variables are defined as follows:

- Date of death as reported on the disposition CRF
- Date of last contact is defined as the last date the patient was known to be alive as derived from different CRF pages (see details in [Section 16.2.5.2](#))
- Date of progression is the first assessment date at which the overall disease response was recorded as PD
- Date of last adequate assessment is the date of the last assessment with overall disease response of CR, PR or SD which was made before an event or a censoring reason occurred. If no post-baseline assessments are available (before an event or a censoring reason occurred) the date of randomization/start of treatment is used.
- Date of next scheduled assessment is the date of the last adequate assessment plus the protocol specified time interval between assessments. This date may be used if back-dating is considered when the event occurred beyond the acceptable time window for the next radiological assessment as per protocol.

Example (if protocol defined schedule of assessments is 3 months): response assessments at baseline - 3 months - 6 months - missing - missing - PD. Date of next scheduled assessment would then correspond to 9 months.

- Date of treatment discontinuation is the last known date subject took study drug (*to be used, if applicable*)

- Date of new anti-cancer therapy is defined as the start date of first new antineoplastic therapy (including medication, radiotherapy, surgery or HSCT)

16.2.4.5.4 Censoring and sensitivity analyses

Censoring reasons

This section outlines the possible censoring reasons for each time to event variables. In order to summarize the various reasons for censoring, the following categories ([Table 16-4](#)) will be calculated for each time to event variable based on the information reported.

Table 16-4 Censoring reasons

Time to event variables	Possible censoring reasons
OS	<ul style="list-style-type: none"> • Alive • Lost to follow-up
PFS, EFS, TTP and DOR	<ul style="list-style-type: none"> • Ongoing without event • Lost to follow-up • Withdrew consent • Death due to reason other than lymphoma (only used for TTP and DOR) • New anti-cancer therapy added • Event documented after two or more missing response assessments (optional, see Table 16-5) • Adequate assessment no longer available¹
LSS	<ul style="list-style-type: none"> • Alive • Lost to follow-up • Death due to reason other than lymphoma

¹ Adequate assessment is defined in [Section 16.2.4.5.3](#). This reason corresponds to any censoring reasons after two or more missing response assessments. This reason will also be used for censor in case of no baseline assessment

Event date, censoring date and sensitivity analyses

This section outlines the possible event and censoring dates for progression ([Table 16-5](#)), as well as addressing the issues of missing response assessments during the study. It is important that the protocol and analysis plan specify the primary analysis in detail with respect to the definition of event and censoring dates and also include a description of one or more sensitivity analyses to be performed.

Based on definitions outlined in [Section 16.2.4.5.2](#), and using the draft FDA guideline on endpoints ([FDA 2007](#)) as a reference, the following analyses can be considered:



Table 16-5 Options for event dates used in PFS, EFS, TTP, DOR

Situation		Options for end-date (progression) ¹ (1) = default unless specified differently in the protocol or analysis plan	Outcome
A	No baseline assessment	(1) Date of randomization/start of treatment ²	Censor
B	Progression at or before next scheduled assessment	(1) Date of progression (2) Date of next scheduled assessment ¹	Event Event
C1	Progression or death due to any reason after exactly one missing assessments	(1) Date of progression (or death) (2) Date of next scheduled assessment ¹	Event Event
C2	Progression or death due to any reason after two or more missing assessments	(1) Date of last adequate assessment ¹ (2) Date of next scheduled assessment ¹ (3) Date of progression (or death)	Censor Event Event
D	No progression	(1) Date of last adequate assessment	Censor
E	Treatment discontinuation due to 'Disease progression' without documented progression, i.e. clinical progression based on investigator claim	(1) N/A (2) Date of discontinuation (visit date at which clinical progression was determined)	Ignored Event
F	New anticancer therapy given	(1) Date of last adequate assessment (2) Date of new anticancer therapy (3) Date of secondary anti-cancer therapy (4) N/A	Censor Censor Event Ignored
G	Death due to reason other than lymphoma	(1) Date of last adequate assessment	Censor (only TTP and DOR)
¹ = Definitions can be found in Section 16.2.4.5.3 . ² = The rare exception to this is if the patient dies no later than the time of the second scheduled assessment as defined in the protocol in which case this is a PFS event at the date of death.			

The primary analysis and the sensitivity analyses must be specified in the Study Protocol. Clearly define if and why options (1) are not used for situations C, E and (if applicable) F.

Situations C (C1 and C2): Progression or death after one or more missing assessments:

The primary analysis is usually using options (1) for situations C1 and C2, i.e.

- (C1) taking the actual progression or death date, in the case of only one missing assessment
- (C2) censoring at the date of the last adequate assessment, in the case of two or more consecutive missing assessments

In the case of two or missing assessments (situation C2), option (3) may be considered jointly with option (1) in situation C1 as sensitivity analysis. A variant of this sensitivity analysis consists of backdating the date of event to the next scheduled assessment as proposed with option (2) in situations C1 and C2.

Situation E: Treatment discontinuation due to 'Disease progression' without documented progression: By default, option (1) is used for situation E as patients without documented PD should be followed for progression after discontinuation of treatment. However, option (2) may be used as sensitivity analysis. If progression is claimed based on clinical deterioration instead

of response assessment by e.g. CT-scan, option (2) may be used for indications with high early progression rate or difficulties to assess the response due to clinical deterioration.

Situation F: New cancer therapy given (except for EFS): the handling of this situation must be specified in detail in the protocol. However, option (1), i.e. censoring at last adequate assessment may be used as a default in this case.

Additional suggestions for sensitivity analyses

Other suggestions for additional sensitivity analyses may include analyses to check for potential bias in follow-up schedules for response assessments, e.g.:

- By assigning the dates for censoring and events only at scheduled visit dates. The latter could be handled by replacing in [Table 16-5](#) the “Date of last adequate assessment” by the “Date of previous scheduled assessment (from baseline)”, with the following definition:

Date of previous scheduled assessment (from baseline) is the date when a response assessment would have taken place, if the protocol assessment scheme was strictly followed from baseline, immediately before or on the date of the last adequate assessment.

The need for these types of sensitivity analyses will depend on the requirements for a specific study and disease area and have to be specified in the Study Protocol or RAP documentation.

16.2.5 Data handling and programming conventions

The following rules should be used and specified in the RAP documentation:

16.2.5.1 Calculation of ‘time to event’ variables

Time to event = enddate - startdate + 1 (in days)

When no post-baseline assessments are available, the date of randomization/start of treatment will be used as enddate (duration = 1 day) when time is to be censored at last assessment, i.e. time to event variables can never be negative.

16.2.5.2 Date of last contact

The date of last contact will be derived for patients alive using the latest complete date among the following:

- Assessment dates (e.g., vital signs assessment, performance status assessment, efficacy assessment, laboratory, pharmacokinetics assessment)
- Medication dates including study medication and antineoplastic therapies administered after study treatment discontinuation
- Adverse events dates
- Last known date subject alive collected on the ‘Survival information’ eCRF
- Randomization date

16.2.5.3 Date of new anti-cancer therapy

The date of new anti-cancer therapy is the date of the first antineoplastic therapy (including medicine, radiotherapy and surgery) reported on the post-treatment antineoplastic therapy CRF or from other sources (e.g., HSCT CRF).

16.2.5.4 Incomplete assessment dates

All investigation dates (e.g., PET-CT scan) must be completed with day, month and year. If one or more investigation dates are incomplete but other investigation dates are available, this/these incomplete date(s) are not considered for calculation of the assessment date (and assessment date is calculated as outlined in [Section 16.2.4.5.3](#)). If all measurement dates have no day recorded, the 1st of the month is used.

If the month is not completed, for any of the investigations, the respective assessment will be considered to be at the date which is exactly between previous and following assessment. If a previous and following assessment is not available, this assessment will not be used for any calculation.

16.2.5.5 Incomplete dates for last contact or death

All dates must be completed with day, month and year. If the day is missing, the 15th of the month will be used for incomplete death dates or dates of last contact.

16.2.6 Appendices

Appendix A: Adaptation for use in maintenance/adjuvant settings

For study populations without measurable disease at baseline (e.g., maintenance), the event of interest is no longer progression but relapse, and the main endpoint is no longer progression-free survival but disease-free survival (see below).

Relapsed disease

Any of the following meets the definition of relapsed disease (RD):

- Any new nodal lesion > 15 mm in any axis (i.e. previously normal lymph node becoming >1.5 cm in any axis) on CT (or MRI) after baseline
- Any discrete extranodal lesion (including liver or spleen) reliably appearing on CT (or MRI) after baseline
- $\geq 50\%$ increase in long axis from baseline of any residual lymph node or mass. A residual lymph node or mass is defined as a previously lymphoma-involved lymph node or mass (>10 mm in short axis (without any upper limit)) that was PET negative at baseline and only reliably detected by baseline CT (or MRI). Note: If a residual lymph node or mass at baseline decreases in size during treatment and becomes normal (i.e. complete disappearance of extranodal mass or ≤ 10 mm in short axis and ≤ 15 mm long axis for nodal mass), then reappearance of an extranodal lesion at the same site or increase of the same nodal mass to > 15 mm in the long axis, will be considered RD and will be recorded as a new lesion.
- Any new bone marrow involvement

- Any new malignant effusion

Disease-free survival

Disease-free survival (DFS) is the time from date of randomization / start of treatment to the date of event defined as the first documented relapse of the disease or death due to any cause. If a patient has not had an event, DFS is censored at the date of the last adequate assessment. Similar censoring rules and reasons as the ones used for PFS can be applied.



16.3 Appendix 3: Modified data reporting by study period

Table 16-6 Data reporting adverse events, concomitant medications, and laboratory values

	From ICF signature (or crossover visit) to safety follow-up visit ¹	Only patients who receive tisagenlecleucel From safety follow-up visit ² until Month 60 or early discontinuation from study
AE and SAE	All, including all laboratory abnormalities deemed clinically significant by the investigator	<ul style="list-style-type: none"> Any non-serious AEs \geq Grade 3 and any SAEs irrespective of Grade with at least a possible causal relationship to tisagenlecleucel The following AEs (i.e., non-serious AE and SAEs, if not otherwise specified) should be reported to Novartis regardless of causality: <ul style="list-style-type: none"> AEs with fatal outcome Events related to a study procedure Serious neurologic disorder Serious or opportunistic infections that fulfill any of the following criteria: <ul style="list-style-type: none"> Require anti-infective treatment Lead to significant disability or hospitalization Need for surgical or other intervention Hepatitis B reactivation Progressive multifocal leucoencephalopathy (PML) Prolonged depletion of normal B cells/ Agammaglobulinemia New occurrence or exacerbation of an autoimmune disorder Hematological disorders (incl. aplastic anemia and bone marrow failure) Positive RCL test result New secondary T cell or non T cell malignancy other than the primary underlying malignancy Vector insertion site sequencing result with a mono or oligoclonality pattern or in a location near a known human oncogene
Concomitant medication	All	<ul style="list-style-type: none"> Treatment related to an AE or SAE from the above mentioned list Mutagenic agents (including cytotoxic drugs) Radiation & antineoplastic therapy (including SCT) Immunoglobulin therapy Immunosuppressive agents (including dose of steroids higher than physiologic replacement therapy doses of steroids (<12 mg/m2/day hydrocortisone or equivalent)) Investigational therapy
Laboratory data	All	<ul style="list-style-type: none"> Record all scheduled labs (per Visit Evaluation Schedule, Table 8-2) Record abnormal lab values that is in the opinion of the investigator related to the list of AEs and SAEs provided above.
<p>1 Patients in arm B who have the safety follow-up visit (indicating the end of AE collection), and then crossover to Arm A should restart AE reporting as described in this table starting at the time of the crossover visit.</p> <p>2 The safety follow-up visit will take place 8 weeks after last treatment administration or prior to starting a new anti-cancer therapy, whichever occurs first.</p>		

16.4 Appendix 4: Liver event and laboratory trigger definitions and follow-up requirements

Table 16-7 Liver event and laboratory trigger definitions

	Definition/ threshold
LIVER LABORATORY TRIGGERS	$3 \times \text{ULN ALT} / \text{AST} \leq 5 \times \text{ULN}$ $1.5 \times \text{ULN} < \text{TBL} \leq 2 \times \text{ULN}$
LIVER EVENTS	ALT or AST $> 5 \times \text{ULN}$ ALP $> 2 \times \text{ULN}$ (in the absence of known bone pathology) TBL $> 2 \times \text{ULN}$ (in the absence of known Gilbert syndrome) ALT or AST $> 3 \times \text{ULN}$ and INR > 1.5 Potential Hy's Law cases (defined as ALT or AST $> 3 \times \text{ULN}$ and TBL $> 2 \times \text{ULN}$ [mainly conjugated fraction] without notable increase in ALP to $> 2 \times \text{ULN}$) Any clinical event of jaundice (or equivalent term) ALT or AST $> 3 \times \text{ULN}$ accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia Any adverse event potentially indicative of a liver toxicity*

*These events cover the following: hepatic failure, fibrosis and cirrhosis, and other liver damage-related conditions; the non-infectious hepatitis; the benign, malignant and unspecified liver neoplasms TBL: total bilirubin; ULN: upper limit of normal

Table 16-8 Follow up requirements for liver events and laboratory triggers

Criteria	Actions required	Follow-up monitoring
Potential Hy's Law case ^a	Discontinue the study treatment immediately (<i>if applicable</i>) Hospitalize, if clinically appropriate Establish causality Record the AE and contributing factors (e.g., concomitant medication, medical history, lab) in the appropriate CRF	ALT, AST, TBL, indirect and direct bilirubin, albumin, Alb, PT/INR, ALP and GGT, until resolution (frequency at investigator discretion)
ALT or AST		
$> 8 \times \text{ULN}$	Discontinue the study treatment immediately (<i>if applicable</i>) Hospitalize if clinically appropriate Establish causality Record the AE and contributing factors (e.g., concomitant medication, medical history, lab) in the appropriate CRF	ALT, AST, TBL, indirect and direct bilirubin, albumin, Alb, PT/INR, ALP and GGT until resolution ^c (frequency at investigator discretion)
$> 3 \times \text{ULN}$ and INR > 1.5	Discontinue the study treatment immediately (<i>if applicable</i>) Hospitalize, if clinically appropriate Establish causality Record the AE and contributing factors (e.g., concomitant medication, medical history, lab) in the appropriate CRF	ALT, AST, TBL, indirect and direct bilirubin, albumin, Alb, PT/INR, ALP and GGT until resolution ^c (frequency at investigator discretion)

Criteria	Actions required	Follow-up monitoring
> 5 to ≤ 8 × ULN	Repeat LFT within 48 hours If elevation persists, continue follow-up monitoring If elevation persists for more than 2 weeks, discontinue the study drug (<i>if applicable</i>) Establish causality Record the AE and contributing factors (e.g., concomitant medication, medical history, lab) in the appropriate CRF	ALT, AST, TBL, indirect and direct bilirubin, albumin, Alb, PT/INR, ALP and GGT until resolution ^c (frequency at investigator discretion)
> 3 × ULN accompanied by symptoms ^b	Discontinue the study treatment immediately (<i>if applicable</i>) Hospitalize if clinically appropriate Establish causality Record the AE and contributing factors (e.g., concomitant medication, medical history, lab) in the appropriate CRF	ALT, AST, TBL, indirect and direct bilirubin, albumin, Alb, PT/INR, ALP and GGT until resolution ^c (frequency at investigator discretion)
> 3 to ≤ 5 × ULN (patient is asymptomatic)	Repeat LFT within the next week If elevation is confirmed, initiate close observation of the patient	Investigator discretion Monitor LFT within 1 to 4 weeks
ALP (isolated)		
> 2 × ULN (in the absence of known bone pathology)	Repeat LFT within 48 hours If elevation persists, establish causality Record the AE and contributing factors (e.g., concomitant medication, medical history, lab) in the appropriate CRF	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
TBL (isolated)		
> 2 × ULN (in the absence of known Gilbert syndrome)	Repeat LFT within 48 hours If elevation persists, discontinue the study drug immediately (<i>if applicable</i>) Hospitalize if clinically appropriate Establish causality Record the AE and contributing factors (e.g., concomitant medication, medical history, lab) in the appropriate CRF	ALT, AST, TBL, indirect and direct bilirubin, albumin, Alb, PT/INR, ALP and GGT until resolution ^c (frequency at investigator discretion) Test for hemolysis (e.g., reticulocytes, haptoglobin, unconjugated [indirect] bilirubin)
> 1.5 to ≤ 2 × ULN (patient is asymptomatic)	Repeat LFT within the next week If elevation is confirmed, initiate close observation of the patient	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
Jaundice	Discontinue the study treatment immediately (<i>if applicable</i>) Hospitalize the patient Establish causality Record the AE and contributing factors (e.g., concomitant medication, medical history, lab) in the appropriate CRF	ALT, AST, TBL, indirect and direct bilirubin, albumin, Alb, PT/INR, ALP and GGT until resolution ^c (frequency at investigator discretion)
Any AE potentially indicative of a liver toxicity*	Consider study treatment interruption or discontinuation (<i>if applicable</i>) Hospitalization if clinically appropriate Establish causality Record the AE and contributing factors (e.g., concomitant medication, medical history, lab) in the appropriate CRF	Investigator discretion

Criteria	Actions required	Follow-up monitoring
^a Elevated ALT/AST > 3 × ULN and TBL > 2 × ULN but without notable increase in ALP to > 2 × ULN ^b (General) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia ^c Resolution is defined as an outcome of one of the following: (1) return to baseline values, (2) stable values at three subsequent monitoring visits at least 2 weeks apart, (3) remain at elevated level after a maximum of 6 months, (4) liver transplantation, and (5) death.		
Based on investigator's discretion investigation(s) for contributing factors for the liver event can include: serology tests, imaging and pathology assessments, hepatologist's consultancy; obtaining more detailed history of symptoms and prior or concurrent diseases, history of concomitant drug use, history of exposure to environmental chemical agents, exclusion of underlying liver disease.		

16.5 Appendix 5: Specific renal alert criteria and actions and event follow-up

Table 16-9 Specific renal alert criteria and actions

Renal Event	Actions
Confirmed serum creatinine increase 25 – 49%	Consider causes and possible interventions Follow up within 2-5 days
Serum creatinine increase $\geq 50\%$ + OR if <18 years old, eGFR ≤ 35 mL/min/1.73 m ²	Consider causes and possible interventions Repeat assessment within 24-48 hours if possible Consider drug interruption or discontinuation unless other causes are diagnosed and corrected Consider patient hospitalization and specialized treatment
New onset dipstick proteinuria $\geq 3+$ OR (Spot) urinary protein-creatinine ratio (PCR) ≥ 1 g/g (or mg/ mmolL equivalent as converted by the measuring laboratory)	Consider causes and possible interventions Assess serum albumin & serum total protein Repeat assessment to confirm Consider drug interruption or discontinuation unless other causes are diagnosed and corrected
New onset hematuria $\geq 3+$ on urine dipstick	Assess & document <ul style="list-style-type: none"> Repeat assessment to confirm Distinguish hemoglobinuria from hematuria Urine sediment microscopy Assess serum creatinine Exclude infection, trauma, bleeding from the distal urinary tract/bladder, menstruation Consider bleeding disorder
*Corresponds to KDIGO criteria for Acute Kidney Injury	

Table 16-10 Follow up of renal events

Assess, document and record in the appropriate CRF <ul style="list-style-type: none"> Urine dipstick and sediment microscopy evidence of DIN: crystals, red blood cells (dysmorphic/glomerular vs. non-dysmorphic/non-glomerular), white blood cells, tubular epithelial cells Blood pressure and body weight Serum creatinine, BUN, electrolytes (sodium, potassium, phosphate, calcium), bicarbonate and uric acid Urine output
Review and record possible contributing factors to the renal event (co-medications, other co-morbid conditions) and additional diagnostic procedures (MRI etc.) in the CRF.
Monitor patient regularly (frequency at investigator's discretion) until: <ul style="list-style-type: none"> Event resolution: serum creatinine within 10% of baseline or PCR <1 g/g or albumin-creatinine ratio <300 mg/g) or <ul style="list-style-type: none"> Event stabilization: serum creatinine level with $\pm 10\%$ variability over last 6 months or PCR stabilization at a new level with $\pm 50\%$ variability over last 6 months Analysis of urine markers in samples collected over the course of the renal event

Clinical Development

CTL019/tisagenlecleucel/Kymriah®

CCTL019H2301

**Tisagenlecleucel versus standard of care in adult patients
with relapsed or refractory aggressive B-cell non-Hodgkin
lymphoma: A randomized, open label, phase III trial
(BELINDA)**

Statistical Analysis Plan (SAP)

Author: Yateman Nigel, Jessie Gu; Trial Statistician
Document type: SAP Documentation
Document status: Final
Release date: 01-May-2019
Number of pages: 52

Property of Novartis
For business use only
May not be used, divulged, published or otherwise disclosed
without the consent of Novartis

Document History – Changes compared to previous final version of SAP

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)

Table of contents

	Table of contents	3
	List of abbreviations	6
1	Introduction	9
1.1	Study design.....	9
1.2	Study objectives and endpoints	11
2	Statistical methods.....	13
2.1	Data analysis general information	13
2.1.1	General definitions	14
2.2	Analysis sets	16
2.2.1	Screened Set	16
2.2.2	Tisagenlecleucel Infused Set.....	17
2.2.3	Full Analysis Set	17
2.2.4	Safety Set	17
2.2.5	Per-Protocol Set	17
2.2.6	Cellular Kinetic Analysis Set	17
2.2.7	Subgroup of interest	18
2.3	Patient disposition, demographics and other baseline characteristics	19
2.3.1	Subject disposition	19
2.3.2	Analysis Sets	19
2.3.3	Basic demographic and background data.....	19
2.3.4	Medical history.....	19
2.3.5	Diagnosis and extent of cancer	20
2.3.6	Protocol deviations.....	20
2.4	Treatments (study treatment, rescue medication, concomitant therapies, compliance).....	20
2.4.1	Study treatment / compliance.....	20
2.4.2	Prior, concomitant and post therapies	21
2.5	Analysis of the primary objective.....	23
2.5.1	Primary endpoint.....	23
2.5.2	Statistical hypothesis, model, and method of analysis	23
2.5.3	Handling of missing values/censoring/discontinuations.....	24
2.5.4	Supportive analyses.....	24
2.6	Analysis of the key secondary objective	25
2.7	Analysis of secondary efficacy objectives.....	25
2.7.1	Secondary endpoints	26
2.7.2	Statistical hypothesis, model, and method of analysis	26

2.7.3	Handling of missing values/censoring/discontinuations.....	28
2.8	Safety analyses.....	28
2.8.1	Analysis and reporting periods.....	28
2.8.2	Adverse events (AEs).....	29
2.8.3	Deaths.....	32
2.8.4	Laboratory data	33
2.8.5	Other safety data	34
2.9	Cellular kinetics endpoints	34
2.10	Immunogenicity	35
2.10.1	Humoral immunogenicity	35
2.10.2	Cellular immunogenicity.....	35
2.11	Patient-reported outcomes	35
2.12	Biomarkers.....	39
2.12.1	Biomarker data analysis set.....	40
2.12.2	Data handling	40
2.12.3	PD-1 and PD-L1 status and other exhaustion markers	40
2.12.4	Soluble immune factors.....	40
2.12.5	MRD by Ig deep sequencing.....	40
2.12.6	Genomic and/or Next Generation Sequencing (NGS) analysis	40
2.12.7	B cell and T cell characterization.....	41
2.12.8	Molecular characteristics of tisagenlecleucel apheresis product /final product	41
2.13	Interim analysis.....	41
3	Sample size calculation	41
4	Change to protocol specified analyses	42
5	Appendix	42
5.1	Imputation rules	42
5.1.1	Study drug	42
5.1.2	AE, ConMeds and safety assessment date imputation.....	43
5.1.3	Dates of initial diagnosis of cancer, first relapse and most recent recurrence/relapse	44
5.1.4	Response assessments	44
5.1.5	Anti-neoplastic therapies.....	45
5.1.6	Date of hospitalization imputation.....	45
5.1.7	Incomplete date for death or last known date subject alive	45
5.2	AEs coding/grading	46
5.3	Laboratory parameters derivations	46

5.4	Derivation of treatment exposure endpoints.....	48
5.4.1	Duration of exposure to chemotherapy.....	48
5.4.2	Cumulative dose.....	48
5.4.3	Dose intensity and relative dose intensity.....	49
5.4.4	Dose reductions, interruptions or permanent discontinuations for ibrutinib/lenolizumab	49
5.5	Statistical models.....	50
5.5.1	Analysis of time-to-event data	50
5.5.2	Analysis of binary data.....	51
6	Reference.....	51

List of abbreviations

ABC	Activated B-cell
AE	Adverse event
AESI	Adverse event of special interest
ASBMT	American society for blood and marrow transplantation
ATC	Anatomical therapeutic chemical
AUC	Area under the curve
Bcl-2	B-cell lymphoma 2
Bcl-6	B-cell lymphoma 6
BEAM	Carmustine, etoposide, cytarabine and melphalan
BIRC	Blinded independent review committee
BOR	Best overall response
CAR	Chimeric antigen receptor
CI	Confidence interval
CK	Cellular kinetic
CKAS	Cellular kinetics analysis set
Clast	Last concentration
Cmax	Maximum concentration
C-myc	C-myc proto-oncogene
CR	Complete response
CRO	Contract research organization
CRP	C-reactive protein
CRS	Cytokine release syndrome
CSF	Cerebral spinal fluid
CSR	Clinical study report
CT	Computerized tomography
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
CV%	Coefficient of variation (%)
DHAP	Cisplatin, cytarabine and dexamethasone
DI	Dose intensity
DLBCL	Diffuse large B-cell lymphoma
DMC	Data monitoring committee
DOR	Duration of response
DRL	Drug reference listing
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
eCRS	Electronic case retrieval strategy
EFS	Event-free survival
EOT	End of treatment
EQ-5D	EuroQol 5 dimension

EQ-VAS	EuroQol visual analogue scale
EWB	Emotional well-being
FACT-G	Functional Assessment of Cancer Therapy – General
FACT-Lym	Functional Assessment of Cancer Therapy – Lymphoma
FAS	Full analysis set
FDG	Fluorodeoxyglucose
FL3B	Follicular lymphoma grade 3B
FWB	Functional well-being
GCB	Germinal center B-cell
HCRU	Health care resource utilization
HDCT	High dose chemotherapy
HR	Hazard ratio
HRQoL	Health related quality of life
HSCT	Hematopoietic stem cell transplant
ICU	Intensive care unit
IL-6	Interleukin 6
IL-10	Interleukin 10
IPI	International prognostic index
IPW	Inverse probability weighting
IRT	Interactive response technology
ITT	Intention to treat
KM	Kaplan-Meier
LD	Lymphodepleting
LLOQ	Lower limit of quantification
LPLV	Last patient last visit
LYMS	Lymphoma-specific subscale
MCS	Mental component summary
MedDRA	Medical Dictionary for Drug Regulatory Affairs
MRA	Magnetic resonance angiography
MRD	Minimum residual disease
MUGA	Multigated acquisition
NCI	National Cancer Institute
NHL	Non-Hodgkin lymphoma
NGS	Next generation sequencing
NOS	Not otherwise specified
ORR	Overall response rate
OS	Overall survival
PCS	Physical component summary
PD	Progressive disease
PD1	Programmed cell death 1
PDI	Planned dose intensity
PDL1	Programmed death ligand 1
PET	Positron emission tomography

PFS	Progression-free survival
PK	Pharmacokinetics
PMBCL	Primary mediastinal large B-cell lymphoma
PPS	Per-protocol set
PR	Partial response
PRO	Patient-reported outcomes
PWB	Physical well-being
QoL	Quality of life
qPCR	Quantitative polymerase chain reaction
RCL	Replication competent lentivirus
RDI	Relative dose intensity
r/r	Relapsed/refractory
R-DHAP	Rituximab plus cisplatin, cytarabine and dexamethasone
R-GDP	Rituximab plus gemcitabine, cisplatin and dexamethasone
R-GemOx	Rituximab plus gemcitabine and oxaliplatin
R-ICE	Rituximab plus ifosfamide, carboplatin, etoposide and mesna
RPSFT	Rank preserving structural failure time
SAE	Serious adverse event
SD	Stable disease
SAP	Statistical analysis plan
SF-36 v2	Short Form (36) Health Survey, version 2
SOC	Standard of care
SWB	Social well-being
T1/2	Time to half life
TFLs	Tables, Figures, Listings
TIS	Tisagenlecleucel infused set
Tlast	Time of last concentration
Tmax	Time to peak concentration
TOI	Trial outcome index
TS	Total score
UNK	Unknown
VSV	Vesicular stomatitis virus
WBC	White blood cells
WHO	World Health Organization

1 Introduction

This Statistical Analysis Plan (SAP) describes the implementation of the statistical analysis planned in the protocol for study CCTL019H2301: Tisagenlecleucel versus standard of care in adult patients with relapsed or refractory aggressive B-cell non-Hodgkin lymphoma: A randomized, open label, phase III trial (BELINDA).

Up to two clinical study reports (CSRs) could result from this SAP:

- Primary analysis: performed after 200 event-free survival (EFS) events have been documented by the blinded independent review committee (BIRC). If statistically significant, this will trigger an interim analysis for overall survival (OS).
- Final analysis: in case the interim analysis of OS is not statistically significant, a final analysis will be performed approximately 5 years after the first patient was randomized.

This SAP is not planned to be used for any other analyses.

The SAP was based on version 01 of the study protocol dated 22-February-2019.

1.1 Study design

This is a randomized, open label, multicenter phase III trial comparing the efficacy, safety and tolerability of tisagenlecleucel treatment strategy versus standard of care (SOC) treatment strategy as second line treatment in adult patients with aggressive B-cell non-Hodgkin lymphoma (NHL). Patients must be refractory/relapsed (r/r) within 12 months of last dose of first line immunochemotherapy, which must contain both rituximab and an anthracycline. Refractory disease is defined as absence of complete response (CR) during first line therapy; relapsed disease is defined as CR on first line therapy followed by progressive disease (PD).

All screened patients will undergo non-mobilized leukapheresis for autologous T cell collection after obtaining informed consent. During the screening period, no lymphoma-specific therapy is allowed prior to randomization.

A subject randomization list has been produced by the Interactive Response Technology (IRT) provider, based on a validated system that automates the random assignment of subject numbers to randomization numbers. Each randomization number is linked to one of the two treatment strategy arms. The randomization is stratified by three binary factors:

- Remission duration: refractory to first line therapy or relapsed < 6 months after last dose of first line therapy versus relapsed 6 - 12 months after last dose of first line therapy
- International Prognostic Index (IPI) score at study entry: < 2 versus ≥ 2
- Region (North America versus Rest of World)

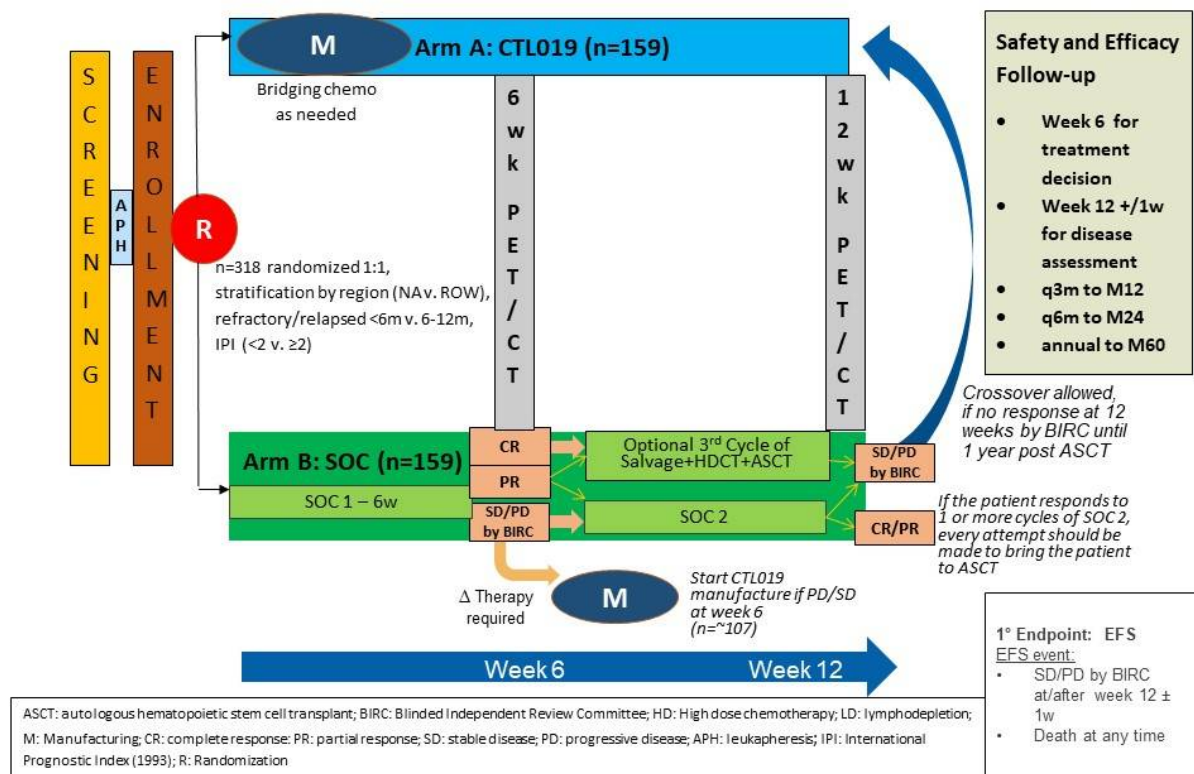
The randomization list has been reviewed and approved by a member of the Novartis Randomization Office. The study design is illustrated in [Figure 1-1](#). Eligible patients will be randomized in a 1:1 ratio within each of the eight strata combinations to one of the following arms:

Arm A: tisagenlecleucel treatment strategy, or tisagenlecleucel arm, consisting of optional bridging chemotherapy and lymphodepleting (LD) chemotherapy followed by a single infusion of tisagenlecleucel. After randomization, tisagenlecleucel is manufactured for the patient, which

is expected to take 3-4 weeks. During this period the use of one of four platinum-based bridging immunochemotherapies is allowed (R-ICE, R-DHAP, R-GDP and R-GemOx). Once the tisagenlecleucel product is released by the manufacturing facility, patients should receive LD chemotherapy for 2 or 3 days duration (not required in patients with significant cytopenia), and then receive the tisagenlecleucel infusion about 5 days later. Thus it is expected that tisagenlecleucel infusion will occur approximately 4 to 6 weeks after randomization. Following infusion of tisagenlecleucel, no further anticancer therapies are allowed.

Arm B: standard of care (SOC) treatment strategy, or SOC arm, consisting of standard of care chemotherapy with transplant. Patients will receive one of four platinum-based immunochemotherapies (R-ICE, R-DHAP, R-GDP and R-GemOx) followed in responding patients by high dose chemotherapy (HDCT) and autologous hematopoietic stem cell transplantation (HSCT). Every effort should be made to perform autologous HSCT in patients achieving a PR, if deemed in the patient's best interest by the treating physician. Patients with response that is not sufficient to allow HSCT should change therapy to one of the other immunochemotherapy regimens listed above, at the investigator's discretion in an attempt to achieve a sufficient response and then proceed to HSCT. Only patients who are deemed no longer eligible for HSCT (e.g., due to adverse event, poor tolerance to immunochemotherapy, worsening of performance status) after two cycles of immunochemotherapy may proceed to lenalidomide or ibrutinib treatment at investigator discretion. If the assessment of SD or PD is confirmed by BIRC at the Week 6 assessment, the investigator may request manufacturing of tisagenlecleucel (but not cross over). In addition, patients with PR FDG+ disease per local assessment at the Week 12 assessment may request manufacturing of tisagenlecleucel. Crossover can only occur following confirmation of SD/PD per BIRC at or after the Week 12 assessment, until 1 year after autologous HSCT.

Figure 1-1 Study design



Tumor response assessments will be performed at baseline (within 2 weeks prior to randomization), and post-baseline at the following times after randomization: weeks 6 (\pm 2 weeks) and 12 (\pm 1 week), months 6, 9 and 12 (\pm 2 weeks), months 18 and 24 (\pm 2 weeks), and thereafter annually (\pm 2 weeks) until 5 years after randomization. Efficacy will be assessed using the Lugano criteria (as detailed in Appendix 2 of the study protocol).

It is planned to randomize a total of 318 patients. The primary endpoint is EFS, and the primary analysis is to be performed after 200 EFS events have been documented. There is no planned interim analysis for EFS, however, an interim analysis for the secondary endpoint of overall survival (OS) will be conducted at the time of the primary analysis, but only if the primary endpoint EFS is statistically significant. If such an interim analysis takes place and OS is not statistically significant, a final analysis for OS will be conducted approximately 5 years after the first patient was randomized.

1.2 Study objectives and endpoints

The primary objective of this study is to compare tisagenlecleucel treatment strategy to standard of care (SOC) treatment strategy with respect to EFS.

The two treatment strategies to be compared are defined as:

- Tisagenlecleucel treatment strategy: optional bridging chemotherapy and lymphodepleting chemotherapy followed by a single infusion of tisagenlecleucel
- Standard of Care (SOC) treatment strategy: SOC immunochemotherapy followed in responding patients by high dose chemotherapy (HDCT) and autologous hematopoietic stem cell transplantation (HSCT)

A list of study objectives and related endpoints are provided in Table 1-1, reproduced from the study protocol:

Table 1-1 Objectives and related endpoints

Objectives	Endpoints
Primary Objective	
<ul style="list-style-type: none"> • To compare tisagenlecleucel treatment strategy to SOC treatment strategy with respect to delaying the composite event of disease progression / stable disease at or after the week 12 assessment; or death at any time. 	<ul style="list-style-type: none"> • EFS, defined as time from date of randomization to the date of first documented disease progression or stable disease at or after the week 12 assessment, as assessed by blinded independent review committee (BIRC) per Lugano criteria, or death at any time
Secondary Objectives	
<ul style="list-style-type: none"> • To compare tisagenlecleucel treatment strategy to SOC treatment strategy with respect to EFS as assessed by local investigator. 	<ul style="list-style-type: none"> • EFS as assessed by local investigator
<ul style="list-style-type: none"> • To compare tisagenlecleucel treatment strategy to SOC treatment strategy with respect to overall survival (OS). 	<ul style="list-style-type: none"> • OS: defined as the time from randomization to date of death
<ul style="list-style-type: none"> • To compare tisagenlecleucel treatment strategy to SOC treatment strategy with respect to overall response rate (ORR) • To evaluate duration of response (DOR) by BIRC and local investigator. 	<p>The following endpoints will be evaluated by BIRC and investigator assessment per Lugano criteria:</p> <ul style="list-style-type: none"> • ORR: overall response rate as per the Lugano criteria • Duration of response: time from the date of first documented response of CR or PR to the date of first documented progression (SD or PD at or after the week 12 assessment will be considered progression) or death due to aggressive B-cell NHL
<ul style="list-style-type: none"> • To evaluate safety and tolerability of tisagenlecleucel treatment strategy versus SOC treatment strategy 	<ul style="list-style-type: none"> • Type, frequency and severity of serious and non-serious adverse events and laboratory abnormalities and discontinuations due to adverse events
<ul style="list-style-type: none"> • To compare patient reported outcomes (PRO) of health-related quality of life (HRQoL) in both treatment arms. 	<ul style="list-style-type: none"> • Time to definitive deterioration in SF-36v2, FACT-Lym, and EQ-VAS
<ul style="list-style-type: none"> • Evaluate efficacy and safety of both treatment arms in histological subgroups (e.g., DLBCL NOS, FL3B, other) and molecular subgroups (e.g. GCB, ABC, other) 	<ul style="list-style-type: none"> • EFS, OS and AE
<ul style="list-style-type: none"> • To characterize the in vivo cellular kinetics of tisagenlecleucel transduced cells into target tissues (blood, bone marrow, cerebral spinal fluid and other tissues if available), as measured by qPCR summarized by clinical response in patients receiving tisagenlecleucel therapy in arm A or after crossover 	<ul style="list-style-type: none"> • Summary of qPCR detected tisagenlecleucel transgene concentrations in peripheral blood and bone marrow (and other tissue, if available), and cellular kinetic parameters from peripheral blood profile samples by time point and clinical response status
<ul style="list-style-type: none"> • To characterize the incidence and prevalence of tisagenlecleucel immunogenicity (humoral and cellular) and impact on cellular kinetics, efficacy, 	<ul style="list-style-type: none"> • Summary of pre-existing and treatment induced immunogenicity (cellular and humoral) of tisagenlecleucel

and safety in patients receiving tisagenlecleucel therapy in arm A or after crossover	<ul style="list-style-type: none"> Levels of pre-existing and treatment induced immunogenicity. Cellular kinetic parameters, concentration-time profile by immunogenicity category (positive/negative), and efficacy (Month 3 response)
<ul style="list-style-type: none"> To assess presence of RCL in patients receiving tisagenlecleucel in arm A or after crossover 	<ul style="list-style-type: none"> RCL by VSV-qPCR
Exploratory Objectives	
<ul style="list-style-type: none"> Characterize the in vivo cellular kinetics (levels or surface expression) of tisagenlecleucel transduced cells in peripheral blood and to target tissues if available as measured from flow cytometry data, in patients receiving tisagenlecleucel therapy in Arm A or after crossover 	<ul style="list-style-type: none"> Summary of surface expression in peripheral blood, bone marrow as appropriate, by time point
<ul style="list-style-type: none"> Characterize and summarize cellular kinetics by use of tocilizumab and also by CRS grade in patients receiving tisagenlecleucel therapy in arm A or after crossover 	<ul style="list-style-type: none"> Cmax, Tmax, AUCs, and other cellular kinetic parameters, use of tocilizumab (YES/NO), and CRS grade
<ul style="list-style-type: none"> To explore the relationship between tisagenlecleucel cellular kinetics, dose, and clinical response (including efficacy and safety) in patients receiving tisagenlecleucel therapy in arm A or after crossover 	<ul style="list-style-type: none"> Parameters: Cmax, Tmax, AUCs, others as appropriate and clinical response parameters (e.g. ORR, DOR, dose)
<ul style="list-style-type: none"> Explore relationship in baseline tumor biopsy specimens between CD19, PD1 and PD-L1 expression, and clinical response in Arm A or after crossover 	<ul style="list-style-type: none"> ORR, DOR, EFS, CD19 expression, PD-1, PD-L1 expression
<ul style="list-style-type: none"> Profile blood soluble markers (e.g. IL-6, gamma interferon) and their correlation with safety and efficacy in Arm A or after crossover 	<ul style="list-style-type: none"> ORR, DOR, EFS and OS, Concentrations of soluble factors in blood, CRS grade and neuronal toxicity
<ul style="list-style-type: none"> Characterize B cell levels over time in both treatment arms and relationship with transgene persistence, clinical response in patients receiving tisagenlecleucel therapy in arm A or after crossover 	<ul style="list-style-type: none"> B cell levels, cellular kinetics, and clinical response
<ul style="list-style-type: none"> Describe the composition of T cell subsets (immunophenotyping in peripheral blood), summarized by clinical response in Arm A or after crossover 	<ul style="list-style-type: none"> ORR, DOR, EFS and OS, CTL019-positive/CD3-positive/ CD4-positive and CTL019-positive/CD3-positive/CD8-positive T cells and other leukocyte subsets
<ul style="list-style-type: none"> Evaluate tisagenlecleucel efficacy in double-hit/triple hit lymphoma patients (Bcl-2, bcl-6 and c-myc expression) in both treatment arms 	<ul style="list-style-type: none"> ORR, DOR, EFS and OS
<ul style="list-style-type: none"> To assess health care resource utilization (HCRU) with respect to hospitalization (i.e. length of stay, frequency), outpatient visit (i.e. frequency), and concomitant medication use for selected adverse events (eg, CRS and Neurological events) in both treatment arms 	<ul style="list-style-type: none"> HCRU with respect to hospitalization, outpatient visits, and concomitant medication use for selected adverse events

2 Statistical methods

2.1 Data analysis general information

The data will be analyzed by Novartis and/or a designated Contract Research Organization (CRO), including the possible interim analysis of OS (an external statistician is not needed for this interim analysis because it can only be performed after the primary analysis of EFS).

SAS version 9.4 or later, and R version 3.0.2 or later, will be used to perform all data analyses and to generate tables, figures and listings.

Data included in the analysis

The primary analysis is the single planned analysis for the primary efficacy endpoint of EFS. A unique data cut-off date will be established after the targeted number of EFS events for the primary analysis (n=200) has been documented. All statistical analyses for the primary analysis will be performed using all data collected in the database up to the data cut-off date. All data with an assessment date or event start date (e.g., vital sign assessment date or start date of an adverse event) prior to or on the cut-off date will be included in the analysis. Any data collected beyond the cut-off date will not be included in the analysis and will not be used for any derivations.

All events with start date before or on the cut-off date and end date after the cut-off date will be reported as 'ongoing'. The same rule will be applied to events starting before or on the cut-off date and not having a documented end date. This approach applies, in particular, to adverse event and concomitant medication reports. For these cases, the end date will not be imputed and therefore will not appear in the listings.

The data cut-off date for the primary analysis will also serve as the data cut-off date for the possible interim analysis of the secondary endpoint of OS. The data cut-off date for the final analysis of OS will be set at 5 years after the randomization of the first patient.

General analysis conventions

Pooling of centers: Unless specified otherwise, data from all study centers will be pooled for the analysis. Due to the expected small number of subjects enrolled at centers, no center effect will be assessed.

Qualitative data (e.g., gender, race, etc.) will be summarized by means of contingency tables by treatment group; a missing category will be included as applicable. Percentages will be calculated using the number of subjects in the relevant population or subgroup as the denominator.

Quantitative data (e.g., age, body weight, etc.) will be summarized by appropriate descriptive statistics (i.e., mean, standard deviation, median, q1, q3, minimum and maximum) by treatment group.

2.1.1 General definitions

2.1.1.1 Treatment strategy

The treatment strategies were defined in [Section 1.2](#) above.

2.1.1.2 Completion of treatment strategy

The tisagenlecleucel treatment strategy is considered completed when the subject is infused with tisagenlecleucel. Subjects are considered as discontinued from the tisagenlecleucel treatment strategy if they discontinue the study without tisagenlecleucel infusion.

The SOC treatment strategy is considered completed when the subject has undergone autologous HSCT following SOC chemotherapy. Subjects are considered as discontinued from the SOC treatment strategy if they discontinue the study without autologous HSCT.

2.1.1.3 Start date of treatment strategy

The start date of treatment strategy is defined as the first date when a non-zero dose of any component of the treatment strategy was administered.

2.1.1.4 End date of treatment strategy

The end date of treatment strategy is defined as the last date when a non-zero dose of any component of study treatment strategy was administered.

For patients in the tisagenlecleucel arm, this can be no later than the date of tisagenlecleucel infusion, and for transplanted patients in the SOC arm, no later than the date of transplantation. In the case of SOC arm patients who do not go to transplant, and who cross over to tisagenlecleucel, the end date of treatment strategy must be before the start of any bridging chemotherapy or lymphodepleting chemotherapy administered prior to tisagenlecleucel infusion.

2.1.1.5 Study day

The study day describes the day of an event/assessment relative to the randomization date, and is defined as:

- (date of event/assessment – date of randomization + 1) if event/assessment is on or after the date of randomization
- (date of event/assessment – date of randomization) if event/assessment precedes the date of randomization. In this case the study day will be negative.

The study day will be displayed in the data listings.

In addition, days from tisagenlecleucel infusion will be calculated and listed for selected analyses of efficacy, safety and cellular kinetics post-tisagenlecleucel infusion.

2.1.1.6 Baseline

For **baseline disease evaluations**, the most current assessments (imaging, pathology assessment, bone marrow biopsy or aspirate, CSF cytology, lesions from physical exam findings, etc.) on or prior to the date of randomization will be used as the baseline assessment. Any imaging or disease assessments obtained after randomization cannot be considered for baseline.

For **safety evaluations** (i.e., AEs, laboratory abnormalities, vital signs, etc.), the last available assessment on or prior to the date of randomization is taken as baseline.

In addition, the last available assessment before the tisagenlecleucel infusion is taken as baseline for selected analyses of safety and cellular kinetics post-tisagenlecleucel infusion.

If patients have no value as defined above, the baseline results will be missing.

2.1.1.7 Duration of study follow-up

Duration from the date of randomization until the analysis cutoff date for the primary analysis, or until the LPLV for the final analysis, will be calculated and summarized.

2.1.1.8 Last contact date

The last contact date will be used for censoring of patients in the analysis of overall survival. For patients not known to have died as of the analysis cut-off date, the last contact date should be derived as the latest date on or before the data cut-off date from the dates listed in the first column of [Table 2-1](#) below. For each of the sources, specific conditions listed in the table have to be fulfilled to ensure that there was true contact with the patient. No additional dates are allowed to be used, for example, dates coming from concomitant medications, PRO, etc.

Table 2-1 Data sources for last contact date

Source data	Conditions
Date of Randomization	No condition
Last date patient was known to be alive from Survival Follow-up page	No condition
Start/End dates from further antineoplastic therapy	Non-missing medication/procedure term
Start/End dates from drug administration record	Non-missing dose
Any specific efficacy assessment date if available	Evaluation is not missing
Laboratory/cellular kinetics collection dates	Sample collection with non-missing value
Vital signs date	At least one non-missing parameter value
Performance Status date	Non-missing performance status
Start/End dates of AE	Non-missing verbatim term

Note: imputed dates will not be used to derive the last contact date with the exception of partially imputed dates from the Survival Follow-up page.

2.1.1.9 Lost to follow-up

For overall survival analysis, patients will be considered as lost to follow-up if the time between their last contact date and the analysis cutoff date is greater than or equal to 105 days (i.e., 3 months plus 2 weeks, assuming 1 month = 30.4375 days).

For response-related time-to-event analyses (i.e., EFS and DOR), patients will be considered as lost to follow-up only if they discontinued the study due to loss to follow-up.

2.2 Analysis sets

The analysis sets to be used are defined as below.

2.2.1 Screened Set

The screened set comprises all subjects who have signed informed consent and were screened in the study.

2.2.2 Tisagenlecleucel Infused Set

The tisagenlecleucel infused set (TIS) comprises all subjects who received infusion of tisagenlecleucel (i.e., including crossover patients from the SOC arm).

The TIS will be used for all efficacy and safety summaries for subjects infused with tisagenlecleucel.

2.2.3 Full Analysis Set

The full analysis set (FAS) comprises all subjects to whom study treatment has been assigned by randomization. According to the intent to treat principle, subjects will be analyzed according to the treatment and strata they have been assigned to during the randomization procedure.

The FAS will be used as the main analysis set for efficacy, demographics and other baseline characteristics.

2.2.4 Safety Set

The safety set comprises all subjects to whom study treatment has been assigned by randomization. Subjects will be analyzed according to randomization.

The safety set will be used for all randomized safety comparisons.

2.2.5 Per-Protocol Set

The per-protocol set (PPS) consists of a subset of subjects in the FAS who are compliant with requirements of the study protocol.

Protocol deviations leading to exclusion from the PPS include:

- Diagnosis of disease other than histologically-confirmed aggressive B-cell NHL
- Relapse/progression more than 12 months after last dose of first line therapy for aggressive B-cell NHL
- Received more than one line of therapy for aggressive B-cell NHL

2.2.6 Cellular Kinetic Analysis Set

The cellular kinetic analysis set (CKAS) consists of subjects in the tisagenlecleucel infused set (TIS) who provide evaluable tisagenlecleucel cellular kinetic data. A subject is considered as having evaluable cellular kinetic data if at least one cellular kinetic parameter can be derived. The CKAS will be used for summaries (tables and figures) of cellular kinetic data. The TIS will be used for listings of cellular kinetic data.

Note that subjects will be removed from the estimation of certain CK parameters on an individual basis depending on the number of available samples. These subjects will be identified at the time of the analyses.

2.2.7 Subgroup of interest

Efficacy

If the primary efficacy analysis based on the FAS is statistically significant, the primary efficacy endpoint of event-free survival (EFS) will be summarized by the following subgroups to examine the homogeneity of the treatment effect:

- Stratification factors, based on the data from eCRF:
 - Remission duration (Refractory or relapsed within 6 months, Relapsed at 6-12 months)
 - IPI at study entry (< 2 , ≥ 2)
 - Geographical region (North America, Rest of the World)
- Age (< 65 years, ≥ 65 years)
- Sex (Male, Female)
- Race (Asian, Black, Caucasian, Other)
- Ethnicity (Hispanic or Latino, Chinese, Indian, Japanese, Mixed ethnicity, Other)
- ECOG performance status (0, 1)
- Histology (e.g., DLBCL NOS, FL3B, PMBCL, High grade lymphoma, Other)
- Rearrangements in MYC/BCL2/BCL6 genes (Double/Triple hits, Other)
- Stage of disease at study entry (I/II, III/IV)
- Molecular: DLBCL cell of origin (Activated B cell, Germinal Center B cell, Other)

No formal statistical test of hypotheses will be performed for the subgroups, only point estimates of the treatment effect and 95%-confidence intervals will be provided (see Sections 2.8.4 and 2.9.4 for further analysis details). The objective of the efficacy subgroup analysis is to demonstrate homogeneity of treatment effect in the above subgroups. Subgroup analyses will only be performed if adequate number of events are observed.

Safety

Key safety analyses on AESIs, deaths, SAEs and AEs leading to discontinuation will be repeated in the safety set, and in the tisagenlecleucel infused set, in the following subgroups:

- Age (< 65 years, ≥ 65 years)
- Sex (Male, Female)
- Race (Asian, Black, Caucasian, Other)
- Ethnicity (Hispanic or Latino, Chinese, Indian, Japanese, Mixed ethnicity, Other)
- Geographical region (North America, Rest of the World)
- IPI at study entry (< 2 , ≥ 2)

The objective for carrying out these subgroup analyses is to identify potential safety issues that may be limited to a subgroup of patients, or safety issues that are more commonly observed in a subgroup of patients. Summary tables will only be performed if at least 5 patients are present in each subgroup. Some grouping of classes will be considered.

2.3 Patient disposition, demographics and other baseline characteristics

Unless specified otherwise, the FAS will be used for all baseline and demographic summaries. Summaries will be reported by treatment arm and for all subjects. The FAS will also be used for listings, where subjects will be presented by treatment arm.

2.3.1 Subject disposition

Subject disposition will be summarized as follows:

- Screening disposition for the screened set
- Treatment disposition for the FAS by treatment arm
- Study disposition for the FAS by treatment arm

For each disposition, subject status including completed, ongoing or discontinued (with reason for discontinuation) will be summarized based on the number and percentage of subjects as listed on the disposition eCRF pages.

Study follow-up will be summarized numerically as well as by categories: <6 months, 6 months to <12 months, 12 months to <24 months, \geq 24 months etc. for the FAS.

All disposition data will be listed using the screened set.

2.3.2 Analysis Sets

The number (%) of subjects in each analysis set (defined in Section 2.2) will be summarized by treatment group and stratum.

2.3.3 Basic demographic and background data

All demographic and baseline disease characteristics data will be summarized and listed by treatment arm. The following grouping will be applied:

- Age: <65 vs. \geq 65 years
- ECOG performance status: 0 vs. 1

Baseline stratification factors

The number (%) of subjects in each stratum, based on data obtained from the eCRF, will be summarized overall and by treatment arm for the FAS. Subgroup analysis using descriptive statistics based on stratification factors will also use data from the eCRF. These analyses may be repeated using data from the IRT system, but only if strata membership differs between IRT and eCRF for at least one patient. For statistical models that are stratified by one or more of the baseline stratification factors, the stratification per IRT will be used.

2.3.4 Medical history

Medical history and ongoing conditions, including cancer-related conditions and symptoms entered on eCRF will be summarized and listed by treatment arm. Ongoing and historical medical conditions will be flagged separately in the listing. The summaries will be presented by primary system organ class (SOC), preferred term (PT) and treatment arm. Medical history

and current medical conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

2.3.5 Diagnosis and extent of cancer

The summary of diagnosis and extent of cancer (i.e., disease history) will include predominant histological subgroup (e.g., DLBCL NOS, FL3B, PMBCL, etc.), stage at initial diagnosis, stage at time of study entry, lines of therapy for prior lymphoma, lines of therapy for current lymphoma, IPI at study entry, DLBCL cell of origin subtype (local), rearrangements in MYC/BCL2/BCL6 genes (e.g. double/triple hits etc.) (local), time (in months) from initial diagnosis of current lymphoma to start of treatment strategy, time (in months) since most recent relapse/progression to start of treatment strategy, time (in months) from initial diagnosis of primary site to most recent relapse/progression, and time (in months) from diagnosis of prior lymphoma to initial diagnosis of current lymphoma (only for patients with prior lymphoma).

Subjects will be classified by their prior treatment response as:

- Refractory: defined as subjects who did not achieve CR or PR on first line therapy to current lymphoma
- Relapsed: defined as subjects who had CR or PR on first line therapy to current lymphoma and relapsed prior to the study

2.3.6 Protocol deviations

The number (%) of subjects in the FAS with any protocol deviation will be tabulated by deviation category (as specified in the study Edit Check document) overall and by treatment group. Major protocol deviations leading to exclusion from analysis sets will be tabulated separately overall and by treatment group. All protocol deviations will be listed.

2.4 Treatments (study treatment, rescue medication, concomitant therapies, compliance)

2.4.1 Study treatment / compliance

2.4.1.1 Tisagenlecleucel arm

The FAS will be used for all summaries and listings of study treatment.

2.4.1.1.1 Tisagenlecleucel

The total viable cell count (cells) and the total CAR-positive viable T cell count (cells) will be listed and summarized using descriptive statistics. Subjects will be categorized as below, within or above the target dose ranges.

Time from screening and randomization to tisagenlecleucel infusion will be summarized using descriptive statistics.

2.4.1.1.2 Lymphodepleting chemotherapy

The lymphodepleting chemotherapies, received after randomization but prior to tisagenlecleucel infusion will be listed. The number and percentage of subjects who received

lymphodepleting chemotherapy will be summarized by therapy type, i.e., fludarabine/cyclophosphamide, bendamustine or other. Duration of exposure (Section 3.4), actual cumulative dose (in mg/m^2) and reason for therapy discontinuation will also be summarized by therapy type.

2.4.1.1.3 Bridging chemotherapy

Bridging chemotherapies are defined as chemotherapies received after randomization but prior to lymphodepleting chemotherapies. The number and percentage of subjects who received bridging chemotherapy will be summarized by therapy type, i.e., R-ICE, R-DHAP, R-GDP, R-GemOx or other. Duration of exposure (Section 5.4.1), number of cycles, dose reduction/interruption/discontinuation and corresponding reasons will also be summarized by therapy type; actual cumulative dose (in mg/m^2), dose intensity ($\text{mg}/\text{m}^2/\text{day}$) and relative dose intensity will be summarized by each component of the bridging chemotherapy regimen.

2.4.1.2 SOC arm

2.4.1.2.1 Immunochemotherapy

The number and percentage of subjects who received chemotherapy will be summarized by therapy type, i.e., R-ICE, R-DHAP, R-GDP or R-GemOx. Duration of exposure (Section 3.4), number of cycles, dose reduction/interruption/discontinuation and corresponding reasons will also be summarized by therapy type; actual cumulative dose (in mg/m^2), dose intensity ($\text{mg}/\text{m}^2/\text{day}$) and relative dose intensity will be summarized by each component of the immunochemotherapy regimen.

2.4.1.2.2 Conditioning chemotherapy

The number and percentage of subjects who received conditioning high dose chemotherapy will be summarized by therapy type, i.e., BEAM or other. Duration of exposure (Section 3.4) and reason for therapy discontinuation will also be summarized by therapy type; actual cumulative dose (in mg/m^2), dose intensity ($\text{mg}/\text{m}^2/\text{day}$) and relative dose intensity will be summarized by each component of the conditioning chemotherapy.

2.4.1.2.3 Autologous HSCT

The number and percentage of subjects who underwent autologous HSCT will be summarized.

2.4.2 Prior, concomitant and post therapies

Medications will be coded using the latest version of World Health Organization (WHO) Drug Reference Listing (DRL) dictionary that employs the WHO Anatomical Therapeutic Chemical (ATC) classification system at the time of analysis; surgical and medical procedures will be coded using MedDRA. The versions of the WHO-DRL and the MedDRA that will be used will be footnoted in all relevant outputs.

Prior anti-cancer therapy

Prior anti-cancer therapy refers to all anti-cancer interventions (therapeutic treatments and procedures) for aggressive B-cell NHL that are administered prior to randomization. The

number and percentage of subjects in the FAS who received any prior anti-cancer medications, prior anti-cancer radiotherapy or prior anti-cancer surgery will be summarized by treatment arm, and listed separately.

New anti-cancer therapy

New anti-cancer therapy consists of anti-cancer therapy administered on or after randomization, excluding therapies given as part of the randomly assigned treatment strategy. As such, new anti-cancer therapy is defined separately for each treatment arm as follows:

In the tisagenlecleucel arm:

- any anti-CD19 or gene therapy other than tisagenlecleucel
- conditioning therapy (high dose chemotherapy) with intention of HSCT
- any anti-neoplastic therapy other than optional bridging chemotherapy (regardless of protocol-specified or not) or lymphodepleting chemotherapy prior to tisagenlecleucel infusion (including for patients who do not go on to receive tisagenlecleucel)
- any anti-neoplastic therapy at any time after tisagenlecleucel infusion

In the SOC arm:

- any anti-CD19 or gene therapy including tisagenlecleucel
- any anti-neoplastic therapy prior to HSCT except SOC treatment options (including patients who do not go to HSCT but are still eligible)
- any anti-neoplastic therapy at any time after HSCT

Please note that local therapies (for example radiation therapy to one specific lesion for symptom control in patients with multiple lesions) may not be considered as new anti-cancer therapy.

New anti-cancer therapies will be listed and summarized by ATC class, preferred term, overall and by treatment arm by means of frequency counts and percentages using the FAS.

Concomitant therapies

Concomitant therapy is defined as all interventions (therapeutic treatments and procedures) given to a subject during the study other than those specified as study treatment. Concomitant therapy includes medications (other than study drugs) starting on or after randomization or medications starting prior to start date of randomization and continuing after the start date of randomization.

Concomitant medications will be summarized by lowest ATC class and preferred term using frequency counts and percentages by treatment arm. Surgical and medical procedures will be summarized by SOC and preferred term.

All concomitant therapies will be listed. Any concomitant therapies starting and ending prior to the start of study treatment will be flagged in the listing. The FAS will be used for all concomitant medication tables and listings.

Anti-cytokine medications are given for severe CRS due to tisagenlecleucel cells. The number of subjects administered with anti-cytokine medications, type of anti-cytokine medications

received, and number of tocilizumab doses given for the management of CRS will be summarized using the FAS.

2.5 Analysis of the primary objective

The primary aim of the study is to compare two second line treatment strategies in adult patients with aggressive B-cell non-Hodgkin lymphoma who are refractory to or relapsed after frontline standard of care and are eligible for stem cell transplantation. The treatment strategies will be compared based on their effect on delaying the composite event of disease progression / stable disease at or after the Week 12 assessment or death at any time. These two treatment strategies will be compared based on all randomized patients, irrespective of whether the patient received all or some of the components of the randomized treatment. Intercurrent events preventing compliance with these strategies such as initiation of alternative cancer therapies prior to the composite event of interest, will be handled accordingly. A Cox regression model stratified by randomization stratification factors will be used to estimate the hazard ratio (HR) of EFS.

2.5.1 Primary endpoint

The primary endpoint of the study is event-free survival (EFS), defined as the time from the date of randomization to the date of the first documented disease progression or stable disease at or after the Week 12 assessment, as assessed by BIRC per Lugano criteria (see Appendix 2 of the study protocol), or death due to any cause, at any time. The protocol-allowed time window for the Week 12 assessment is +/- 1 week; however, as an analysis convention, response assessments as early as week 10 will be taken into account as valid Week 12 assessments (i.e., on or after study day 71, where study day 1 is the date of randomization). This approach is taken in case some patients have an early Week 12 assessment, for example to avoid delaying future study treatment options, e.g., HSCT in the SOC arm, tisagenlecleucel infusion in the tisagenlecleucel arm. Censoring conventions are provided in [Section 2.5.3](#).

2.5.2 Statistical hypothesis, model, and method of analysis

The primary efficacy analysis will be the comparison of the distribution of EFS between the two treatment strategies in the FAS. Assuming proportional hazards for EFS, the following statistical hypothesis will be tested to address the primary efficacy objective:

$$H_0: \theta_1 \geq 1 \text{ vs. } H_{A1}: \theta_1 < 1$$

where θ_1 is the EFS hazard ratio (tisagenlecleucel arm versus standard-of-care arm). The analysis to test this hypothesis will consist of a stratified log-rank test at an overall one-sided 2.5% level of significance. Stratification will be based on the randomization stratification factors, as assigned in IRT, of remission duration (refractory or relapsed within 6 months vs. relapsed at 6-12 months), IPI score at study entry (< 2 vs. ≥ 2) and region (North America vs. Rest of the World).

There will be no interim analysis for EFS. The final analysis for EFS will be performed on the data observed in the FAS up to the data cut-off date, after approximately 200 EFS events have been documented by the BIRC. The study will be considered positive if the stratified log-rank test performed at the final analysis for EFS has a one-sided p-value ≤ 0.025 .

The survival distribution of EFS will be estimated using the Kaplan-Meier method and will be plotted graphically by treatment arm. The median EFS along with its 95% confidence interval will be presented by treatment arm. The survival probabilities at 3, 6, 9 and 12 months, and the associated 95% confidence intervals, will be summarized by treatment arm. A stratified Cox regression model will be used to estimate the hazard ratio (HR) of EFS, along with its 95% confidence interval, using the same strata as for the primary efficacy comparison.

2.5.3 Handling of missing values/censoring/discontinuations

The analysis of EFS will be based on all randomized patients, regardless of whether the patient received all or some of the components of the randomized treatment, and the amount of dose received.

If no EFS event is observed prior to the earliest censoring event, EFS will be censored. Censoring events include loss to follow-up, withdrawal of consent, data cut-off date and initiation of new anticancer therapy (as defined in [Section 2.4.2](#)). If the earliest censoring event occurs before the Week 12 assessment, then EFS will be censored at the date of the censoring event (since only death counts as an EFS event prior to the Week 12 assessment). If the earliest censoring event occurs after the Week 12 assessment, then EFS will be censored at the date of the last assessment with CR/PR prior to the earliest censoring event and on or after the Week 12 assessment. In the case where the Week 12 assessment has a response of “unknown” and the censoring event occurs before any further response assessment with CR/PR, EFS will be censored on the day before the Week 12 assessment.

2.5.4 Supportive analyses

Patients in the tisagenlecleucel arm are only expected to receive tisagenlecleucel infusion between 4 and 6 weeks after randomization (see [Section 1.1](#)), and before the infusion they may be receiving bridging chemotherapy, consisting of one of the four chemotherapy regimens planned for the SOC arm. As such, any efficacy benefit to the tisagenlecleucel arm is only anticipated to emerge after 4-6 weeks. This delayed treatment effect is an example of non-proportional hazards, and can lead to a loss of power for the stratified log-rank test, the primary analysis in the study. Therefore as a supportive analysis, a weighted stratified log-rank test will be used to compare EFS per BIRC assessment between the tisagenlecleucel and SOC arms, as follows:

- Piece-wise weighted log-rank test [[Xu et al 2017](#)]: assigning weights of 0 to event times in the first 6 weeks, and weights of 1 thereafter.

The test will be conducted at the one-sided 2.5% level, and be stratified by the randomization stratification factors of remission duration, IPI score at study entry and region. In addition, the treatment effect will be summarized by the average hazard ratio (and 95% CI) obtained from a weighted stratified Cox model, stratified by the randomization stratification factors.

Further supportive analyses will include:

- Hazard ratio and 95% CI of EFS per BIRC from an unstratified Cox model without any covariate adjustment
- Hazard ratio and 95% CI of EFS per BIRC from a stratified Cox model, stratified by the randomization stratification factors of remission duration, IPI at study entry and region,

and adjusted for the following possibly prognostic covariates: age, gender, race, ECOG performance status, histological subgroup, stage of disease at study entry and DLBCL subtype

- EFS per BIRC review in the Per Protocol Set, using the same analyses as in the primary efficacy analysis (with the exception of the log-rank test, which will not be performed)
- EFS per local investigator review, using the same analyses as in the primary efficacy analysis, with the exception of the log-rank test which will not be performed (this was one of the secondary objectives of the study, see [Section 1.2](#))

Also depending on the amount of missing assessments, further sensitivity analyses maybe undertaken, for example, censoring EFS after two or more missing response assessments.

If the primary analysis is statistically significant, subgroup analyses to assess the homogeneity of the treatment effect across demographic and baseline disease characteristics will be performed. The list of subgroups is provided in [Section 2.2.7](#). The analyses will include Kaplan-Meier summaries of median EFS with 95% CI by treatment arm, and stratified Cox models will be used to estimate EFS hazard ratios and their 95% CIs. Only subgroups with an adequate number of events (at least 5) will be included. Note that even if the primary analysis is not statistically significant, the above subgroup analyses will be undertaken for both the histological and molecular subgroups, because this is a stated secondary objective of the study (see [Section 1.2](#)).

The number of subjects censored and reasons for censoring will be summarized by treatment arm using descriptive statistics, presented separately for EFS per BIRC and EFS per local investigator review.

Stratified log-rank tests and Cox regression models will be repeated for the following alternative definitions of EFS:

- EFS per BIRC irrespective of new anti-cancer therapy for lymphoma, i.e., EFS events will be counted even if occurring after start of a new anti-cancer therapy. This corresponds to a fully intention-to-treat approach for both treatment strategies
- EFS per BIRC considering new anti-cancer therapy for lymphoma at any time as an EFS event.

2.6 Analysis of the key secondary objective

There is no key secondary objective in this study.

2.7 Analysis of secondary efficacy objectives

The secondary efficacy objectives are to compare tisagenlecleucel treatment strategy to SOC treatment strategy with respect to:

- Event-free survival (EFS) as assessed by local investigator (already discussed in [Section 2.5.4](#) as supportive analysis for primary objective)
- Overall survival (OS)
- Overall response rate (ORR), both by BIRC and local investigator assessment
- Duration of response (DOR), both by BIRC and local investigator assessment

- EFS as assessed by BIRC and OS in histological subgroups (DLBCL NOS, FL3B, PMBCL, etc) and molecular subgroups (e.g., GCB, ABC, other)

2.7.1 Secondary endpoints

Overall survival

Overall survival (OS) is defined as the time from date of randomization to date of death due to any cause. A cut-off date will be established for each analysis of OS. All deaths occurring on or before the cut-off date will be used in the OS analysis. If a patient is not known to have died at the data cut-off date, OS will be censored at the date of last contact.

Overall response rate

Overall response rate (ORR) is defined as the proportion of subjects with best overall response (BOR) of complete response (CR) or partial response (PR) according to the Lugano criteria (see Appendix 2 of the study protocol for details).

BOR is defined as the best overall disease response from the sequence of overall disease responses, observed between the Week 12 assessment and the first to occur between the data cut-off date, the start date of a new anticancer therapy (as defined in [Section 2.4.2](#)) and the date of EFS event. That is, response assessments before the Week 12 assessment are not used in the calculation of BOR, in order to maintain consistency with the definition of EFS used in this study. For example, a patient with overall disease response of PD at Week 6 followed by CR at Week 12, would have a BOR of CR. Response assessments as early as week 10 (study day 71) will be taken into account as valid Week 12 assessments.

Duration of response

Duration of response (DOR) only applies to patients whose best overall response is complete response (CR) or partial response (PR) according to the Lugano criteria. It is defined as the time from the date of first documented response of CR or PR, to the date of the first subsequent documented progression or death due to aggressive B-cell NHL. In this study, “documented progression” refers to a response of SD or PD on or after the Week 12 assessment, and assessments on or after week 10 (study day 71) will be considered as valid Week 12 assessments. Censoring conventions are provided in [Section 2.7.3](#).

2.7.2 Statistical hypothesis, model, and method of analysis

Overall survival

OS will only be tested if the primary endpoint (EFS as assessed by BIRC) is statistically significant at the primary analysis for EFS. In that case, and assuming proportional hazards for OS, the following statistical hypotheses will be tested in the FAS:

$$H_{02}: \theta_2 \geq 1 \text{ vs. } H_{A2}: \theta_2 < 1$$

where θ_2 is the OS hazard ratio (tisagenlecleucel arm versus standard-of-care arm). The analysis to test this hypothesis will consist of a stratified log-rank test at an overall one-sided

2.5% level of significance. Stratification will be based on the randomization stratification factors: remission duration, IPI score at study entry and region.

If the EFS primary endpoint is statistically significant, OS will be analyzed using a group sequential design with two looks, the first at the time of the primary analysis for EFS, and the second at 5 years after the randomization of the first patient. A Haybittle-Peto boundary will be used, where the one-sided significance level is 0.05% at the interim analysis and 2.5% at the final analysis. Analyses will be based on the FAS according to the randomized treatment group and stratum assigned at randomization.

Irrespective of whether the EFS primary endpoint is statistically significant or not, the following analyses will be undertaken. The distribution of OS will be estimated using the Kaplan-Meier method, and Kaplan-Meier curves will be presented. The median OS and the proportion of patients alive at 6 and 12 weeks, and at 6, 12, 18, 24, 36, 48 and 60 months, with 95% confidence intervals, will be presented by treatment arm. The hazard ratio for OS will be calculated, along with its 95% confidence interval, using a Cox model stratified by the randomization stratification factors.

Subgroup analyses will be undertaken for histological subtype and molecular subgroup, because these are a stated secondary objective of the study (see [Section 1.2](#)). The analyses will include Kaplan-Meier summaries of median OS with 95% CI by treatment arm, and stratified Cox models will be used to estimate OS hazard ratios and their 95% CIs.

The number of subjects censored for OS and reasons for censoring will be summarized by treatment arm using descriptive statistics.

Overall response rate

ORR based on BIRC assessment will be summarized using descriptive statistics (N, %) by treatment arm, along with two-sided standard Wald asymptotic (i.e., normal approximation) 95% CIs. As a supportive analysis, ORR will also be summarized based on the local investigator assessment of response data. In addition, comparative summary of best overall response between BIRC assessment and local assessment will be provided to evaluate the consistency of the two results.

Furthermore, a descriptive summary of response status after bridging chemotherapy and before tisagenlecleucel infusion for Arm A patients will be provided.

Duration of response

DOR will be summarized by treatment arm for all patients in the FAS with BOR of CR or PR. The distribution of DOR will be estimated using the Kaplan-Meier method, and Kaplan-Meier curves will be presented. The median DOR and the proportion of patients remaining relapse-free at 3, 6, 12, 18, 24, 36, 48 and 60 months after first response, with 95% confidence intervals, will be presented by treatment arm. The hazard ratio for DOR will be calculated, along with its 95% confidence interval, using a Cox model stratified by the randomization stratification factors of remission duration, IPI at study entry and region.

2.7.3 Handling of missing values/censoring/discontinuations

Overall survival

If a patient is not known to have died at the data cut-off date, OS will be censored at the date of last contact (see [Section 2.1.1.8](#) for definition of last contact date).

Patients in the SOC arm are allowed to crossover to tisagenlecleucel treatment, subject to certain specific conditions (see [Section 1.1](#)). The primary analysis of OS will be based on the intent-to-treat (ITT) principle, so that patients randomized to the SOC arm who receive tisagenlecleucel will still be counted in the SOC arm for the analysis. Whilst this ITT approach provides a valid estimate to compare the two treatment strategies, it may underestimate the possible benefit of the tisagenlecleucel treatment strategy (for example, compared with the treatment effect that would have been observed in the absence of crossover). As supportive analyses for OS, methods for analysis that take account of crossover will be performed, including the rank preserving structural failure time model (RPSFT) and inverse probability weighting (IPW). These methods will be described in a separate document.

Overall response rate

Patients with unknown or missing best overall response (BOR) will be counted as non-responders. If there is no baseline response assessment, all post-baseline overall disease responses are expected to be Unknown. If no valid post-baseline response assessments are available, the best overall response will be Unknown unless progression is reported. For the computation of ORR, these patients will be counted as non-responders.

Duration of response

If no DOR event (i.e., SD/PD on or after the Week 12 assessment or death due to aggressive B-cell NHL) is observed prior to the earliest censoring event, DOR will be censored. The same censoring reasons used in the primary EFS analysis will be used for DOR, with the addition of “death due to reason other than aggressive B-cell NHL”. The censoring date will be the date of the last assessment with response of CR or PR on or prior to the earliest censoring event.

2.8 Safety analyses

The main focus of the safety analyses are:

- to compare the safety of the two treatment strategies as defined in [Section 1.2](#) in the safety set
- to evaluate safety post-tisagenlecleucel infusion in the tisagenlecleucel infused set.

The safety analyses will be based on the analysis sets specified above unless specified otherwise.

2.8.1 Analysis and reporting periods

Note that following the definitions in [Table 2-3](#) below, the **safety comparison period** will be the main safety reporting period for the randomized safety comparison, and the **post-infusion period** will be the main safety reporting period for the evaluation of safety after tisagenlecleucel infusion.

Table 2-2 Safety reporting periods

Period	Definition	Subjects to be included
For both arms		
Screening period *	From the day of subject's informed consent to the day before randomization	Screened set
Safety comparison period	From the day of randomization to the earlier day of starting a new anticancer therapy, or 56 days after last study treatment administration	Safety set
Post safety-comparison period	From the day after the earlier day of starting a new anticancer therapy, or 56 days after last study treatment administration, until end of study	Safety set
For tisagenlecleucel arm and subjects in SOC arm with a crossover visit		
Pre-lymphodepleting period **	From day of randomization (subjects in tisagenlecleucel arm) or day of crossover visit (subjects in SOC arm with a crossover visit) to the day before first lymphodepleting chemotherapy dose or the day before infusion of tisagenlecleucel if lymphodepleting chemotherapy is not given	Full analysis set
Lymphodepleting period ***	From the first day of lymphodepleting chemotherapy to <ul style="list-style-type: none"> the day before infusion of tisagenlecleucel, for subjects who received infusion, or the earlier of date of discontinuation and 30 days after last dose of lymphodepleting chemotherapy for subjects who didn't receive infusion of tisagenlecleucel 	All subjects who received lymphodepleting chemotherapy
Post-infusion period	Starting on the day of the first tisagenlecleucel infusion until end of study	Tisagenlecleucel infused set
<p>* If a subject was not randomized, all the AEs for the subject are considered to be in the screening period.</p> <p>** If a subject did not receive lymphodepleting chemotherapy or tisagenlecleucel infusion, all the AEs for the subject are considered to be in the pre-lymphodepleting period.</p> <p>*** This period only applies to subjects who received lymphodepleting chemotherapy.</p>		

2.8.2 Adverse events (AEs)

Reporting of adverse events follows the modified safety reporting rules described in Protocol Appendix 3.

Reporting of AEs (except for CRS) will be based on MedDRA (latest version per database lock) and the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. The grading of CRS will be primarily based on the Lee criteria [Lee et al 2014].

- For the randomized safety comparison, AE summaries will include all AEs that started or worsened during the safety comparison period, i.e. **post-randomization** AEs.
- For the safety evaluation post-tisagenlecleucel infusion, AE summaries will include all AEs that started or worsened during the post-infusion period, i.e. **tisagenlecleucel-treatment-emergent** AEs.

AEs will be summarized by number and percentage of subjects with at least one AE, at least one AE in each primary system organ class and for each preferred term. A subject with multiple occurrences of an AE will be counted only once in the respective AE category. A subject with multiple CTCAE grades for the same preferred term will be summarized under the maximum CTCAE grade recorded for the event. AE with missing CTCAE grade will be included in the all grades column of the summary tables. The frequency of AEs of grade 3 or above will be summarized together.

In AE summary tables, the primary system organ class will be presented alphabetically and preferred terms will be sorted within the primary system organ class in descending frequency. The sort order for the preferred terms will be based on their frequency in the 'All grades' column as reported in the tisagenlecleucel arm.

For the **randomized safety comparison**, the following adverse event summaries will be produced by treatment arm in subjects from the safety set for the safety comparison period:

- Overview of adverse events, deaths, and other serious or clinically significant AEs
- Adverse events, regardless of study treatment relationship, by primary system organ class, preferred term and maximum grade
- Adverse events, suspected to be study treatment related, by primary system organ class, preferred term and maximum grade
- Serious adverse events, regardless of study treatment relationship, by primary system organ class and preferred term and maximum grade
- Serious adverse events, suspected to be study treatment related, by primary system organ class and preferred term and maximum grade
- Adverse events leading to study treatment discontinuation, regardless of study treatment relationship, by primary system organ class and preferred term
- Adverse events leading to study treatment interruption/adjustment, regardless of study treatment relationship, by primary system organ class and preferred term
- Non-serious adverse events, regardless of study treatment relationship, by primary system organ class and preferred term

For the **safety evaluation post-tisagenlecleucel infusion**, the adverse event summaries listed below will be produced separately for subjects in Arm A and subjects crossed over from Arm B to Arm A from the tisagenlecleucel infused set for the post-infusion period by timing of onset: within 8 weeks of first tisagenlecleucel infusion, >8 weeks to 1 year after the first tisagenlecleucel infusion, >1 year after the first tisagenlecleucel infusion, and any time after the first tisagenlecleucel infusion. The denominator for each time period will be the number of subjects still remaining in the study at the start of the corresponding time period.

- Overview of adverse events, deaths, and other serious or clinically significant AEs

- Adverse events, regardless of tisagenlecleucel relationship, by primary system organ class, preferred term and maximum grade
- Adverse events, suspected to be tisagenlecleucel related, by primary system organ class, preferred term and maximum grade
- Serious adverse events, regardless of tisagenlecleucel relationship, by primary system organ class and preferred term and maximum grade
- Serious adverse events, suspected to be tisagenlecleucel related, by primary system organ class and preferred term and maximum grade
- Non-Serious Adverse events, regardless of tisagenlecleucel relationship, by primary system organ class and preferred term

In addition, the following AEs will be summarized:

- All AEs that started or worsened within 2 days of the leukapheresis procedure for all subjects who received leukapheresis
- All AEs that started or worsened during the pre-lymphodepleting period, and separately for subjects who did or did not receive bridging chemotherapy during the pre-lymphodepleting period
- All AEs that started or worsened during the lymphodepleting period

2.8.2.1 Adverse events of special interest / grouping of AEs

AESIs include all important identified and potential risks of tisagenlecleucel, and may also include additional relevant safety topics (e.g., missing information or exploratory safety topics). The list of AESIs and their search criteria are updated on a regular basis at program level in the electronic Case Retrieval Strategy (eCRS) form. The most recent version of the eCRS form will be used for the reporting activity.

For the **randomized safety comparison**, the AESIs will be summarized by treatment arm in the safety comparison period, in subjects from the safety set.

For the **safety evaluation post-tisagenlecleucel infusion**, AESIs will be summarized separately for subjects in Arm A and subjects crossed over from Arm B to Arm A by drug relationship, group term, preferred term, maximum grade and timing of onset in subjects from the tisagenlecleucel infused set for the post-infusion period by timing of onset: within 8 weeks of first tisagenlecleucel infusion, >8 weeks to 1 year after the first tisagenlecleucel infusion, >1 year after first tisagenlecleucel infusion, and any time after first tisagenlecleucel infusion.

AESI based on important identified risks and potential risks will be summarized in post-text tables by timing of onset:

- AESI post-tisagenlecleucel infusion based on important **identified** risks, regardless of study drug relationship, by group term, preferred term and maximum CTC grade
- AESI post-tisagenlecleucel infusion based on important **potential** risks, regardless of study drug relationship, by group term, preferred term and maximum CTC grade

For in-text tables, AESI based on important identified risks will be summarized for AEs occurring within 8 weeks after first tisagenlecleucel infusion.

2.8.2.1.1 Cytokine release syndrome (CRS)

Detailed information regarding the first episode of CRS, including maximum CRS grade, time to onset of CRS, time to resolution of CRS, time to grade 3/4/5 CRS, concurrent infections, timing and duration of ICU stay, selected complications and use of anti-cytokine therapies, will be summarized by treatment arm. Time to resolution of the first CRS episode will be summarized for subjects with CRS using Kaplan-Meier methodology. In case the end date of an episode of CRS is missing, it will be censored as the minimum of the cut-off date, end of study evaluation date and death date (if applicable).

Note that CRS grades will be primarily reported according to the Lee criteria (Lee et al 2014). Additionally, CRS will also be assessed using other grading scales (e.g., ASBMT consensus grading) and a sensitivity analysis will be conducted.

2.8.2.1.2 Neurological events

Neurological events refer to a group of neurological AEs defined in the AESI search criteria form. A neurological event episode may include multiple overlapping or consecutive neurological AEs as long as the end date and the start date of two consecutive AEs are no more than 3 days apart (i.e., current AE start date – previous AE end date ≤ 3). The onset day of a neurological event episode is the start date of the first neurological AE in the episode. The resolution date is the end day of the last AE in the episode. If there are multiple AEs with the same last end date and one or more of these AEs are unresolved, the entire episode will be considered unresolved. Time to onset of the first neurological event episode will be summarized descriptively. Time to resolution of all neurological event episodes from all subjects will be summarized using Kaplan-Meier methodology, without taking into account that multiple episodes might be clustered by subject. For example, for a subject with two episodes, both episodes will be included in the analysis. Although these two episodes from one subject are not independent, they will be treated as if they are from two subjects (each with one episode).

Neurological events will be reported according to the CTCAE v5.0. Additionally, neurological events will also be assessed using other grading scales (e.g., ASBMT consensus grading) and a sensitivity analysis will be conducted.

2.8.2.1.3 Hematopoietic cytopenias not resolved by day 28

For hematopoietic cytopenias not resolved by day 28, analysis of laboratory results will also be performed (Section 2.8.3) in addition to the analysis of AEs reported by the investigator.

2.8.3 Deaths

Summary tables for deaths will be produced by treatment arm, system organ class and preferred term.

For the **randomized safety comparison**, summary tables for deaths will be provided by treatment arm for all deaths occurring in the safety set during the safety comparison period, i.e., from randomization until the earlier date of starting a new anticancer therapy and 56 days after last study treatment administration.

For the **safety evaluation post-tisagenlecleucel infusion**, summary tables for deaths will be provided separately for subjects in Arm A and subjects crossed over from Arm B to Arm A for all deaths in the tisagenlecleucel infused set that occurred after tisagenlecleucel infusion, by timing of death: within 30 days of tisagenlecleucel infusion, >30 days after tisagenlecleucel infusion and any time after tisagenlecleucel infusion.

All deaths will be listed, and study period as defined in Section 2.8.1 will be flagged in the listings.

2.8.4 Laboratory data

For the analysis of laboratory abnormalities, data from central and local laboratories will be combined.

For laboratory tests covered by the CTCAE, Novartis will assign the appropriate CTC grade to each laboratory value. For laboratory tests where grades are not defined by CTCAE, results will be graded by the low/normal/high classification based on laboratory normal ranges.

The following summaries will be produced for hematology and biochemistry laboratory data (by laboratory parameter and treatment arm):

- Shift tables using CTC grades to compare baseline to the worst post-infusion or safety comparison period value
- For laboratory tests where CTC grades are not defined, shift tables using the low/normal/high classification to compare baseline to the worst post-infusion or safety comparison period value.

For the **randomized safety comparison**, the shift tables will be generated for the safety comparison period in subjects from the safety set.

For the **safety evaluation post-tisagenlecleucel infusion**, the shift tables for the tisagenlecleucel arm will be generated separately for subjects in Arm A and subjects crossed over from Arm B to Arm A from the tisagenlecleucel infused set by timing: within 8 weeks of first tisagenlecleucel infusion, >8 weeks to 1 year after first tisagenlecleucel infusion, >1 year after first tisagenlecleucel infusion, and any time after first tisagenlecleucel infusion.

In addition, for the safety evaluation post-tisagenlecleucel infusion, the percentage of subjects with hematopoietic cytopenia 28-days post-tisagenlecleucel infusion of grade 3 or above will be summarized. Among these subjects, the timing of resolution to grade 2 or below will be presented via Kaplan-Meier methodology. The grading of cytopenias will be derived using laboratory results in absolute lymphocytes (hypo), absolute neutrophils (hypo), hemoglobin (hypo), platelet count (hypo) and WBC (hypo) according to CTCAE 5.0 ([Section 3.3](#)). If a subject did not achieve resolution at the last laboratory assessment, timing of resolution will be censored at that time. The Kaplan-Meier median time to resolution and estimates of the percentage of unresolved cases at different time points (e.g., month 2, month 3, etc.) will be presented.

2.8.5 Other safety data

2.8.5.1 ECG and cardiac imaging data

For ECG data, the number of patients meeting or exceeding predefined limits in terms of absolute QT/QTc intervals or changes from baseline will be presented, separately for subjects in the safety set and the tisagenlecleucel infused set. In addition, listings of these subjects will be produced by treatment arm.

All ECG data will be listed by treatment arm, subject and visit, and abnormalities will be flagged. Cardiac imaging data (ECHO/MRA/MUGA) will be listed.

2.8.5.2 Vital signs

All vital signs data will be listed by treatment group, subject and visit, and if ranges are available, abnormalities will be flagged. Summary statistics will be provided by treatment arm and visit for subjects in the safety set, and by visit for subjects in the tisagenlecleucel infused set.

2.9 Cellular kinetics endpoints

Tisagenlecleucel concentrations in peripheral blood (and bone marrow and CSF if available) will be listed, graphed and summarized (arithmetic and geometric means, standard deviation, CV%, CV% geometric mean, minimum, median and maximum) by time points for subjects in the cellular kinetic analysis set (CKAS) as assessed by the following:

- Tisagenlecleucel transgene levels as measured by q-PCR
- Tisagenlecleucel transduced cells measured by flow cytometry of CD3-positive/CD4-positive and CD3-positive/CD8-positive tisagenlecleucel transduced cells if feasible.

The cellular kinetics parameters listed in [Table 2-4](#) along with other relevant cellular kinetics parameters will be estimated, if feasible, from the individual concentration versus time profiles using a non-compartmental approach within the modeling program Phoenix® (Pharsight, Mountain View, CA) and reported by Month 3 response category. The non-quantifiable concentrations will be imputed to zero for concentration summaries, and will not be included for estimation of cellular kinetics parameters. Results reported but deemed unreliable will be flagged and excluded from the summaries and cellular kinetics parameter derivations.

Table 2-3 Non compartmental cellular kinetics parameters

Parameter	Definition
AUC 0 - 28d and/or AUC0-84d	The AUC from time zero to day 28 and/or day 84 and or other disease assessment days, in peripheral blood (days*copies/ µg)
Cmax	The maximum (peak) observed in peripheral blood or other body fluid drug concentration after single dose administration (copies/ µg)
Tmax	The time to reach maximum (peak) peripheral blood or other body fluid drug concentration after single dose administration (days)
T1/2	The half-life associated with the elimination phase slope of a semi logarithmic concentration-time curve (days) in peripheral blood
Clast	The last observed quantifiable concentration in peripheral blood (copies/ug)
Tlast	The time of last observed quantifiable concentration in peripheral blood (days)

Descriptive statistics of cellular kinetics parameters (arithmetic and geometric means, standard deviation, CV%, CV% geometric mean, minimum, median and maximum) will be summarized by Month 3 response for subjects in the CKAS. For T_{\max} and T_{last} only minimum, median and maximum will be presented.

The relationship between tisagenlecleucel cellular kinetics and dose and response will be explored using appropriate logistic regression and Cox regression models if sufficient data is available in the TIS.

For subjects who receive tocilizumab for management of CRS, the cellular kinetic parameters based on qPCR data will be summarized by use of tocilizumab and CRS grades.

2.10 Immunogenicity

The humoral immunogenicity assay measures the antibody titers specific to the tisagenlecleucel molecule prior to and following infusion. Data will be further fractionated to determine proportion of subjects who make transient versus sustained antibody responses. The cellular immunogenicity assay assesses the presence of T lymphocytes activated by the tisagenlecleucel protein. Data will be reported as summary statistics of pre and post-dose levels of activated T lymphocytes.

The analysis of immunogenicity will be performed separately for patients received tisagenlecleucel in Arm A, or patients crossed over from Arm B to Arm A and infused with tisagenlecleucel.

2.10.1 Humoral immunogenicity

The proportion of humoral immunogenicity positive and negative patients will be summarized by time points. Summary statistics will be presented for tisagenlecleucel cellular kinetic parameters for qPCR by anti- tisagenlecleucel antibody post-infusion status (positive or negative).

A scatter plot of baseline anti-tisagenlecleucel antibodies versus qPCR AUC0-28d and Cmax will be presented along with the appropriate regression line and equation. In addition boxplots of anti- tisagenlecleucel antibodies at enrollment by Month 3 disease response will be presented. The same response categories will be used for a similar boxplot summarizing the maximum fold change of anti-tisagenlecleucel post-infusion.

The plot of tisagenlecleucel transgene concentration-time profile will be presented by post-infusion anti-tisagenlecleucel antibody status.

2.10.2 Cellular immunogenicity

The cellular immunogenicity will be summarized by time points separated for tisagenlecleucel Pool 1 Peptides and tisagenlecleucel Pool 2 peptides. The boxplot of maximum fold change of cellular immunogenicity by Month 3 disease response will be presented. The scatter plot of maximum fold change versus qPCR AUC0-28d and Cmax will also be presented along with the appropriate regression line and equation.

2.11 Patient-reported outcomes

Three separate patient-reported outcome (PRO) instruments will be used in the study:

- FACT-Lym: Functional Assessment of Cancer Therapy – Lymphoma, version 4, to assess lymphoma-specific quality of life. It is composed of the FACT-General (FACT-G), a 27-item questionnaire of general questions, and the FACT-Lym lymphoma-specific subscale (FACT-Lym LymS), an additional 15 items that assess patient concerns relating to lymphoma. All questions are scored on a 5-point scale ranging from 0 = “not at all” to 4 = “very much”; negatively worded questions are reverse-scored so that higher scores are always reflective of better health-related quality of life (HRQoL). FACT-G items are divided into four primary domains: PWB (Physical Well-Being; seven items; range, 0–28), SWB (Social Well-Being; seven items; range, 0–28), EWB (Emotional Well-Being; six items; range, 0–24), and FWB (Functional Well-Being; seven items; range, 0–28). The FACT-Lym LymS consists of common lymphoma disease and/or treatment-related symptoms (e.g., pain, fever, swelling, night sweats, insomnia, itching, weight loss, fatigue and loss of appetite). Three summary scales: FACT-Lym TOI (Trial Outcome Index; range, 0–116; composed of the PWB, FWB, FACT-Lym LymS); FACT-G (range, 0–108; composed of the PWB, FWB, SWB, EWB), and the FACT-Lym TS (Total Score; range, 0–168; composed of all of the scales) are also calculated.
- EQ-5D-5L: EuroQol 5D, to assess health utility for the purpose of economic evaluation. It is composed of the EQ-VAS, a visual analogue scale from 0-100 with higher values indicating better HRQoL, and the EQ-5D assessing five dimensions of health state (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) on an ordinal scale with five categories: “no”, “slight”, “moderate”, “severe” and “extreme”.
- SF-36v2: Short Form (36) Health Survey, version 2, to assess general health and quality of life. It is composed of 36 questions making 8 domains (physical functioning, role – physical, bodily pain, general health, vitality, social functioning, role – emotional, mental health), from which two overall component scores are obtained: PCS (Physical Component Summary) and MCS (Mental Component Summary). Domain and component summary scores are converted to norm-based scores based on the general population, with higher scores indicative of better HRQoL. The scoring of the questionnaire will be provided by the vendor for this instrument.

For missing items within any questionnaire, prorated scores will be calculated according to developer guidance.

The PRO instruments are planned to be administered at randomization and at the following times post-randomization: weeks 6 and 12, months 6, 9, 12, 18 and 24, and annually thereafter until year 5. In addition, for SOC patients who crossover to tisagenlecleucel, PRO assessments post-crossover are planned at: weeks 6, 8 and 12, months 6, 9, 12, 18 and 24, and annually thereafter. Also, for patients with a progression event (SD/PD per BIRC on or after the Week 12 assessment), PRO assessments should be repeated at 4 and 12 weeks after the event, and 6 months after the event. [nth Windows for multiple a31923](#)

Compliance to the schedule of administration for each of the FACT-Lym, EQ-5D-5L and SF-36v2 will be summarized by treatment arm at each time-point in the FAS. The number and percentage of patients completing each instrument will be presented by time-point, based on the number of patients still alive at the scheduled assessment day. Data listings will provide details of whether a questionnaire was completed at each time-point, using the following categories, as collected on the eCRF:

- yes, fully completed
- yes, partly completed
- no, patient missed scheduled assessment visit
- no, patient refused due to poor health
- no, patient refused (unrelated to health)
- no, study staff felt patient was too ill
- no, questionnaire not available in appropriate language
- no, institutional error
- no, other

All subscale, summary and domain scores from the FACT-Lym, the EQ-VAS and the SF-36v2 will be tabulated and displayed as mean profiles for each treatment arm in the FAS, presented over time by scheduled visit. Only data up to the time of new antineoplastic therapy will be considered (as defined in [Section 2.4.2](#)). Change from baseline in the subscale scores at the time of each assessment will also be summarized, where baseline is defined as the last PRO assessment on or prior to randomization.

For patients in the SOC arm who crossover to the tisagenlecleucel arm, post-crossover PRO subscale, summary and domain scores will be tabulated and displayed as mean profiles, presented over time by scheduled visit. Change from baseline in PRO scores at the time of each assessment will also be summarized, where baseline is defined as the last PRO assessment on or prior to the crossover visit (as recorded in the IRT system).

Similarly, for patients in the FAS with a progression event (SD/PD per BIRC on or after the Week 12 assessment), mean profiles and summary tables for all PRO subscale, summary and domain scores will be presented by scheduled visit. Change from baseline will be included, where baseline is defined as the last PRO assessment prior to the progression event.

For each of the five dimensions of the EQ-5D-5L, the proportions of patients in each treatment arm in the FAS having reported “no”, “slight”, “moderate”, “severe” and “extreme” problems will be tabulated at each time-point. One analysis will only include data up to the time of new antineoplastic therapy (as defined in [Section 2.4.2](#)). A second analysis will only include data collected on or after the crossover visit.

Change from baseline item scores means and 95% CIs will be plotted by visit and by treatment arm. Cumulative distribution plots of changes from baseline by treatment group at each visit will be presented, as recommended by FDA guidance on patient-reported outcome measures (FDA, 2009). These plots display a continuous change from baseline on the x-axis and the cumulative percentage of patients experiencing that change on the y-axis.

Time to definitive deterioration

A secondary objective of the study is to compare the treatment arms with respect to the PRO scores. The FACT-Lym TOI will be the primary score for this objective. In addition, the FACT-Lym LymS, FACT-Lym TS and FACT-G will be analyzed as secondary scores, as will the EQ-VAS from the EQ-5D-5L, and the PCS and MCS from the SF-36v2. Note that treatment

comparisons based on hypothesis tests will be considered as descriptive only, and no adjustment for multiple testing will be performed.

The primary PRO endpoint will be time to definitive deterioration, defined as the time from randomization to the date of definitive deterioration. For FACT-Lym TOI, a clinically meaningful deterioration is defined as a decrease from baseline of at least 5.5 points, and the decrease is considered definitive if there is no later improvement above this threshold. The date of definitive deterioration is the earliest such post-baseline assessment. In the absence of an earlier definitive deterioration, patients are censored at the date of the last assessment before the earliest to occur between the data cut-off, start of new anti-neoplastic therapy, and for patients on the SOC arm, the date of crossover visit. Patients with no baseline data will be censored at day 1.

Death is considered as a definitive deterioration when it occurs within a period of time defined by twice the period between two assessments as planned in the study protocol. This avoids overestimating the time to definitive worsening in patients dying after an irregular assessment scheme. Patients who die after more than twice the planned period between two assessments since the last assessment are censored at the date of their last available questionnaire.

Time to definitive deterioration in the FACT-Lym TOI will be compared between the two treatment arms in the FAS using a stratified log-rank test at the one-sided 2.5% level of significance. The test will be stratified by the randomization stratification factors of remission duration, IPI score at study entry and region, as assigned at randomization in IRT. The survival distributions will be presented descriptively using Kaplan-Meier curves. Summary statistics from the Kaplan-Meier distributions will be determined, including the median time to definitive deterioration, and the probabilities of remaining without definitive deterioration at 3, 6, 9 and 12 months. Both point estimates and 95% CIs will be presented. A stratified Cox regression model will be used to estimate the hazard ratio of time to deterioration, along with its 95% confidence interval.

Similar analyses of time to definitive deterioration will be performed on the secondary PRO scales of interest as listed above, with deterioration defined as a decrease from baseline of ≥ 2.9 points for FACT-Lym LymS, ≥ 6.5 points for FACT-Lym TS, ≥ 3 points for FACT-G, ≥ 7 points for EQ-VAS, and ≥ 3 points for both PCS and MCS. Sensitivity analysis may be conducted for PCS and MCS using ≥ 5 as the MCID.

Repeated measure mixed-modeling

As a secondary PRO analysis, repeated measures mixed-modeling will be used to estimate differences in PRO scores between treatment arms in the FAS. The FACT-Lym TOI will be the primary score for this objective. In addition, the FACT-Lym LymS, FACT-Lym TS and FACT-G will be analyzed as secondary scores, as will the EQ-VAS from the EQ-5D-5L, and the PCS and MCS from the SF-36v2.

The analysis will be restricted to patients in the FAS with a baseline score and at least one post-baseline score. All data collected until the data cut-off, start of new anti-neoplastic therapy, or for patients on the SOC arm, the date of crossover visit, will be included in the analysis.

Each model will have an intercept term, a linear time trend term (in weeks), a term for treatment arm, a baseline covariate, and a term for treatment-by-time interaction. Repeated measures over

time will be accounted by unstructured covariance structure (using the REPEATED statement in PROC MIXED). If the model cannot converge with the unstructured covariance structure, a spatial covariance structure will be considered and, if that does not converge, an autoregressive heterogeneous, autoregressive, or compound symmetry variance/covariance matrix will be applied (in that order). All parameter estimates will be obtained using restricted maximum likelihood estimation.

The intercept and slope terms for time will be random effects with an assumed unstructured variance/covariance matrix. In addition, each observation is assumed to be measured with error and the error terms are independent of each other. A sandwich estimator will be used to estimate the variance of the fixed effects terms. All parameter estimates will be obtained using restricted maximum likelihood estimation.

Improvement rates

Improvement rate will also be considered a secondary PRO endpoint, and will be calculated as the proportion of patients in each arm achieving a particular increase from baseline in PRO score. Improvement rates will be calculated at each post-baseline time-point, and compared between the treatment arms at each time-point using the two-sided chi-squared test at the 5% level of significance. These tests are considered descriptive and results exploratory, so no adjustment for multiple testing will be implemented. Improvement is defined as an increase from baseline of ≥ 5.5 points for FACT-Lym TOI, ≥ 2.9 points for FACT-Lym LymS, ≥ 6.5 points for FACT-Lym TS, ≥ 3 points for FACT-G, ≥ 7 points for EQ-VAS, and ≥ 3 points for both PCS and MCS. Sensitivity analysis may be conducted for PCS and MCS using ≥ 5 as the MCID.

2.12 Biomarkers

As a project standard, Novartis Oncology Biostatistics and Data Management will analyze only biomarkers collected in the clinical database. Studies are often not adequately powered to assess specific biomarker-related hypotheses, and for this reason the exploratory biomarker analyses that will be undertaken should be considered as promoting the generation of new scientific hypotheses or observing new trends. These hypotheses may be compared with results found in the literature, as well as verified with data derived from subsequent clinical trials. No adjustment for multiple comparisons is usually planned for exploratory analyses. Additional post hoc exploratory assessments are expected and may be performed.

Additional analysis may be performed after the completion of the end-of-study CSR and will be documented in separate reports. These analyses may include, but are not limited to, the meta-analysis of data from this study combined with data from other studies, or the analysis of biomarkers generated from samples collected during the study but analyzed after database lock and completion of the CSR. The data analysis will be described in an addendum of the SAP or in a stand-alone analysis plan document, as appropriate.

There may be circumstances when a decision is made to stop sample collection, or not perform or discontinue the analysis due to either practical or strategic reasons (e.g., issues related to the quality and/or quantity of the samples, or issues related to the assay). Under such circumstances, the number of samples may be inadequate to perform a rigorous data analysis and the available data will only be listed and potentially summarized.

2.12.1 Biomarker data analysis set

The Full Analysis Set will be used for all biomarker analysis. Unless otherwise specified, all statistical analyses of biomarker data will be performed on patients with biomarker data.

2.12.2 Data handling

Serum cytokine values below the lower limit of quantitation (which may be reported with the label Lower Limit of Quantification [LLOQ]) or have a numerical value below the assay's lower limit of quantification) will be imputed / replaced as $0.5 \times \text{LLOQ}$, which will be specified by the performing laboratory and is assay- and analyte-specific. In cases when an actual value below LLOQ is reported, this value should not be used and the data should be imputed as $0.5 \times \text{LLOQ}$.

2.12.3 PD-1 and PD-L1 status and other exhaustion markers

CD19 expression in tumor biopsy specimens at baseline, PD-1 and PD-L1 expression levels and their interaction score if available will be listed and summarized for Arm A and crossover patients. CD19, PD-1, PD-L1 and PD-1/PD-L1 interaction score will also be summarized by clinical response for Arm A and progressive disease patients.

2.12.4 Soluble immune factors

The profile of blood soluble proteins and inflammatory cytokines and receptors (IL-10, interferon gamma, IL-6, CRP, and ferritin) will be listed and summarized by patient and time point for Arm A and crossover patients. Baseline and absolute and relative change (percent and or fold change) from baseline will be calculated for each time point and summarized using sample size, mean, standard deviation, median, minimum and maximum. If both the baseline and post baseline values are below Lower Limit of Quantification (LLOQ), absolute, percent and fold change from baseline will not be imputed and reported as missing. Baseline levels may also be summarized by clinical response status and relevant adverse events and potentially graphed using strip plots. In addition, the maximum change from baseline measure for each cytokine may also be graphed against clinical response status and relevant adverse events using strip plots. Patient level and averaged cytokine measures and percent change from baseline may be displayed using longitudinal plots.

2.12.5 MRD by Ig deep sequencing

MRD by Ig deep sequencing may be used to identify the dominant tumor clone sequence in blood at baseline and to track clearance or re-appearance of the same clone sequence in subsequent analysis time points. The tumor clonal distribution may be listed for Arm A and crossover patients and percent change from baseline will be summarized if applicable. Patient level absolute and relative changes may be displayed using longitudinal plots. Association between MRD and clinical outcome may be performed.

2.12.6 Genomic and/or Next Generation Sequencing (NGS) analysis

Genomic and/or NGS analysis in relation with clinical endpoints will be performed and documented in separate reports.

Potential analysis exploring relationship of efficacy/safety endpoints with tumor cells mutation and/or gene expression could be also conducted. Analysis of leukocyte transcriptome changes pre and post tisagenlecleucel administration and the correlations between apheresis/cell product and clinical responses (efficacy, safety and cellular kinetic parameters) will be summarized in a separate report.

2.12.7 B cell and T cell characterization

The levels of blood B and/or T cells will be listed and summarized by patient and time point for all enrolled patients. Absolute number and/or frequencies of total B cell populations will be listed and summarized by patient and time point. Baseline and change from baseline to minimum cell number may also be summarized by response status and potentially graphed using strip plots.

T cell subsets by immunophenotyping within tisagenlecleucel positive and/or tisagenlecleucel negative populations will be explored in relation to safety and efficacy endpoints for Arm A and crossover patients. Data may also be summarized by response status and CRS severity and potentially graphed using strip plots. Patient level and average longitudinal plots of the cell counts and percent changes from baseline may be generated.

2.12.8 Molecular characteristics of tisagenlecleucel apheresis product /final product

Apheresis product and/or final product molecular read-outs (e.g. immune cell subsets, T cell differentiation and exhaustion markers, gene expression) will be assessed, listed and summarized by clinical response and/or relevant adverse events for Arm A and crossover patients and summarized in a separate report.

2.13 Interim analysis

No interim analysis is planned for this trial for the primary endpoint of EFS. A hierarchical testing procedure will be adopted and the statistical test for OS will be performed only if the primary efficacy endpoint, EFS is statistically significant.

A maximum of two analyses are planned for OS: 1) an interim analysis at the time of the primary analysis for EFS (provided EFS is significant, as outlined in [Section 2.7.2](#)) in the FAS, and 2) a final analysis for OS at approximately 5 years from the first patient randomized. A Haybittle–Peto boundary will be used for testing OS, where the one-sided significance level is 0.05% at the interim analysis and 2.5% at the final analysis. [nth_Overall_survival64212](#)

3 Sample size calculation

Based on the data from the ORCHARRD study (Novartis unpublished analyses), EFS time for patients who were randomized to receive salvage chemotherapy (DHAP plus Rituximab or DHAP plus Ofatumumab), who never reached CR before or relapsed within 12 months from response to previous therapy, or had a response of PR, SD or PD to previous therapy was considered as a reference for SOC. In ORCHARRD study, for these patients, who continue to be in SD status at the end of cycle 2/3 (which is earlier than the 12 week assessment, each cycle: 21 days) or had progressed earlier than the 12 week assessment, based on the definition of EFS

endpoint used in BELINDA (where documented SD/PD at the Week 12 assessment is considered an EFS event), EFS event time was adjusted to 12 weeks, to account for these earlier events.

The 9 month EFS rate is estimated to be 22.32% in SOC arm and is assumed to be 40% in tisagenlecleucel arm. Due to delayed tisagenlecleucel infusion of 6 weeks and ignoring SD/PD at week 6, we assume piecewise hazard rate in both treatment arms. The hazard ratio between two arms during the first 6 weeks is assumed to be 1 and 0.61 after 6 weeks. Given those assumptions, a total of 200 EFS events are required to have 92% power at an one-sided 2.5% level of significance to reject the null hypothesis (i.e. the survival functions for EFS in the two arms are identical), using a stratified log-rank test with equal weights. The sample size calculation was conducted via simulation with software package East 6.4.

Based on a recruitment period of approximately 21 months using staggered enrollment rates of 2, 10, and 16 patients in the 1st 3 months followed by 17 patients thereafter, and assuming 15% drop out rate, a total of approximately 318 patients will need to be randomized to the two treatment arms in a 1:1 ratio. Given the above assumptions, it is estimated that the 200th EFS event will be observed at approximately 23 months from the date of first patient randomized.

4 Change to protocol specified analyses

1. In Section 2.4.2, definition of new anti-cancer therapy for SOC arm: protocol specified that:
 - any anti-neoplastic therapy prior to HSCT except protocol-allowed-SOC treatment options (including patients who do not go to HSCT).

After discussion with clinical, team feels that SOC treatments even if not protocol allowed, if taken prior to HSCT or for those who do not go to HSCT but are still eligible, is a protocol deviation but should not be considered as new anti-cancer therapy. Accordingly, the following updates have been made in the SAP:

- any anti-neoplastic therapy prior to HSCT except SOC treatment options (including patients who do not go to HSCT but are still eligible)
2. Added a safety subgroup analysis based on IPI at study entry (< 2 , ≥ 2), which may be a prognostic factor of the safety outcome.

5 Appendix

5.1 Imputation rules

5.1.1 Study drug

The following rule should be used for the imputation of the dose end date for a given study treatment component:

Scenario 1: If the dose end date is completely missing and there is no EOT page and no death date, the subject is considered as on-going:

The subject should be treated as on-going and the cut-off date should be used as the dose end date.

Scenario 2: If the dose end date is completely or partially missing and the EOT page is available:

Case 1: The dose end date is completely missing, and the EOT completion date is complete, then this latter date should be used.

Case 2: Only Year(yyyy) of the dose end date is available and yyyy < the year of EOT date:

Use Dec31yyyy

Case 3: Only Year(yyyy) of the dose end date is available and yyyy = the year of EOT date:

Use EOT date

Case 4: Both Year(yyyy) and Month (mm) are available for dose end date, and yyyy = the year of EOT date and mm < the month of EOT date:

Use last day of the Month (mm)

All other cases should be considered as a data issue and the statistician should contact the data manager of the study.

After imputation, compare the imputed date with start date of treatment, if the imputed date is < start date of treatment:

Use the treatment start date

Subjects with missing start dates are to be considered missing for all study treatment component related calculations and no imputation will be made. If start date is missing then end-date should not be imputed.

5.1.2 AE, ConMeds and safety assessment date imputation

Table 5-1 Imputation of start dates (AE, CM) and assessments (LB, EG, VS)

Missing Element	Rule
day, month, and year	<ul style="list-style-type: none"> No imputation will be done for completely missing dates
day, month	<ul style="list-style-type: none"> If available year = year of study treatment start date then <ul style="list-style-type: none"> If stop date contains a full date and stop date is earlier than study treatment start date then set start date = 01JanYYYY Else set start date = study treatment start date. If available year > year of study treatment start date then 01JanYYYY If available year < year of study treatment start date then 01JulYYYY

Missing Element	Rule
day	<ul style="list-style-type: none"> • If available month and year = month and year of study treatment start date then <ul style="list-style-type: none"> ○ If stop date contains a full date and stop date is earlier than study treatment start date then set start date= 01MONYYYY. ○ Else set start date = study treatment start date. • If available month and year > month and year of study treatment start date then 01MONYYYY • If available month and year < month year of study treatment start date then 15MONYYYY

Table 5-2 Imputation of end dates (AE)

Missing Element	Rule
day, month, and year	<ul style="list-style-type: none"> • Completely missing end dates (incl. ongoing events) or with end date on or after the cutoff date will be imputed by min(cutoff date, end of study evaluation, date of death, withdrawal of consent date)
day, month	<ul style="list-style-type: none"> • If partial end date contains year only, set end date = min(31DEC, cutoff date, end of study evaluation, date of death, withdrawal of consent date)
day	<ul style="list-style-type: none"> • If partial end date contains month and year, set end date = min(last day of the month, cutoff date, end of study evaluation, date of death, withdrawal of consent date)

Partial or missing ConMeds end dates will not be imputed.

Any AEs and ConMeds with partial/missing dates will be displayed as such in the data listings.

Any AEs and ConMeds which are continuing as per data cut-off will be shown as ‘ongoing’ rather than the end date provided.

Note that if the imputed AE start date is after the AE end date (regardless of if the end date is imputed or not), use the AE end date as the imputed AE start date.

5.1.3 Dates of initial diagnosis of cancer, first relapse and most recent recurrence/relapse

If the day or month of initial diagnosis, first relapse or most recent relapse is missing, it will be imputed to the minimum of the informed consent date -1 and the following:

- Missing day: 15th day of the month and year
- Missing day and month: July 1st of the year

5.1.4 Response assessments

All investigation dates for response (e.g., dates of PET scan, CT scan, bone marrow biopsy) must be completed with day, month and year. At any response assessment, if one or more investigation dates are incomplete, the response assessment date is calculated from the complete

investigation dates as follows: if the overall disease response at that assessment is CR/PR/SD/UNK, then the assessment date is assigned as the latest complete investigation date, otherwise if overall disease response is PD, then the assessment date is the earliest complete investigation date at that assessment. If no investigation dates at a particular response assessment have day recorded, the 1st of the month is used. If month is not recorded at any of the investigations at a particular response assessment, the response assessment date will be imputed to the mid-point between the previous and following assessments. If a previous and following assessment are not available, this response assessment will not be used for any calculation.

5.1.5 Anti-neoplastic therapies

5.1.5.1 Prior therapies

Start date:

The same rule which is applied to the imputation of AE/concomitant medication start date will be used with the exception that for scenario (B) will be replaced to be 'start date of study treatment -1'.

End date:

Imputed date = min (start date of study treatment, last day of the month), if day is missing;

Imputed date = min (start date of study treatment, 31DEC), if month and day are missing.

If the end date is not missing and the imputed start date is after the end date, use the end date as the imputed start date.

If both the start date and the end date are imputed and if the imputed start date is after the imputed end date, use the imputed end date as the imputation for the start date.

5.1.5.2 Post therapies

Start date:

Imputed date = max (last date of study treatment + 1, first day of the month), if day is missing;

Imputed date = max (last date of study treatment + 1, 01JAN), if day and month are missing.

End date: No imputation.

5.1.6 Date of hospitalization imputation

Missing hospitalization end date or end date after data cutoff will be imputed following the same conventions as for AE end date imputation.

5.1.7 Incomplete date for death or last known date subject alive

If the day or month of death is missing from the death CRF, death will be imputed to the maximum of the full (non-imputed) last contact date ([Section 2.1.1.8](#)) and the following:

- Missing day: 15th day of the month and year of death

- Missing day and month: July 1st of the year of death

If the day or month of last known date subject alive is missing in the survival CRF, it will be first imputed with the following:

- Missing day: minimum of the date of assessment and 15th day of the month and year of last known date subject alive
- Missing day and month: minimum of the date of assessment and July 1st of the year of last known date subject alive

Then the above imputed last known date subject alive will be used to calculate the last contact date as defined in [Section 2.1.1.8](#).

5.2 AEs coding/grading

Adverse events are coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

AEs will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0, except for CRS, where grading of CRS will be primarily based on the Lee criteria [[Lee et al 2014](#)]

The CTCAE represents a comprehensive grading system for reporting the acute and late effects of cancer treatments. CTCAE grading is by definition a 5-point scale generally corresponding to mild, moderate, severe, life threatening and death. This grading system inherently places a value on the importance of an event, although there is not necessarily proportionality among grades (a grade 2 is not necessarily twice as bad as a grade 1).

5.3 Laboratory parameters derivations

Grade categorization of laboratory values will be assigned programmatically as per NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. The calculation of CTCAE grades will be based on the observed laboratory values only, clinical assessments will not be taken into account. The criteria to assign CTCAE grades are given in Novartis internal criteria for CTCAE grading of laboratory parameters per [Table 5-3](#).

For laboratory tests where grades are not defined by CTCAE version 5.0, results will be graded by the low/normal/high (or other project-specific ranges, if more suitable) classifications based on laboratory normal ranges.

A severity grade of 0 will be assigned for all non-missing laboratory values not graded as 1 or higher. Grade 5 will not be used. For laboratory tests that are graded for both low and high values, summaries will be done separately and labelled by direction, e.g., sodium will be summarized as hyponatremia and hypernatremia.

Table 5-3 CTC grades for laboratory values based on CTCAE v5

CTC grades for laboratory values in Novartis Oncology (based on CTCAE v5 – Nov 2017)

Page 1

				CTC Grades ⁽¹⁾				
Lab test (toxicity)	SI unit	Lab test (NCDS)	Normal ranges (Merck manual, July 2015) and <i>conversion factors</i>	0	1	2	3	4
Hematology								
WBC ↓ WBC (Leukocytosis)	10 ⁹ /L 10 ⁹ /L	WBC WBC	3.9 – 10.7 x 10 ⁹ /L	≥ LLN	< LLN - 3.0 x 10 ⁹ /L -	< 3.0 – 2.0 x 10 ⁹ /L -	< 2.0 – 1.0 x 10 ⁹ /L > 100 x 10 ⁹ /L	< 1.0 x 10 ⁹ /L -
Hemoglobin (Anemia)	g/L	HGB	120 - 160 g/L or 7.4 - 9.9 mmol/L (F) 140 - 170 g/L or 8.7 – 10.6 mmol/L (M) (16.113 x mmol/L = g/L)	≥ LLN	< LLN - 100 g/L < LLN - 6.2 mmol/L	< 100 - 80 g/L < 6.2 - 4.9 mmol/L	< 80 g/L < 4.9 mmol/L	-
Hemoglobin ↑	g/L	HGB			Increase > 20 g/L above ULN	Increase > 20-40 g/L above ULN	Increase > 40 g/L above ULN	-
Platelets ↓	10 ⁹ /L	PLAT	150 - 350 x 10 ⁹ /L	≥ LLN	< LLN - 75.0 x 10 ⁹ /L	< 75.0 - 50.0 x 10 ⁹ /L	< 50.0 - 25.0 x 10 ⁹ /L	< 25.0 x 10 ⁹ /L
Neutrophils ↓	10 ⁹ /L	NEUT		≥ 2x10 ⁹ /L	< 2.0 - 1.5 x 10 ⁹ /L	< 1.5 - 1.0 x 10 ⁹ /L	< 1.0 - 0.5 x 10 ⁹ /L	< 0.5 x 10 ⁹ /L
Lymphocytes ↓ Lymphocytes ↑	10 ⁹ /L 10 ⁹ /L	LYM LYM		≥ 1.5x10 ⁹ /L	< 1.5 - 0.8 x 10 ⁹ /L -	< 0.8 - 0.5 x 10 ⁹ /L > 4 - 20 x 10 ⁹ /L	< 0.5 - 0.2 x 10 ⁹ /L > 20 x 10 ⁹ /L	< 0.2 x 10 ⁹ /L -
Biochemistry								
AST ↑	U/L	AST	0 - 35 U/L or 0 – 0.58 ukat/L (60 x ukat/L = U/L)	≤ ULN	> ULN – 3.0 x ULN	> 3.0 - 5.0 x ULN	> 5.0 - 20.0 x ULN	> 20.0 x ULN
ALT ↑	U/L	ALT	0 - 35 U/L or 0 – 0.58 ukat/L (60 x ukat/L = U/L)	≤ ULN	> ULN – 3.0 x ULN	> 3.0 - 5.0 x ULN	> 5.0 - 20.0 x ULN	> 20.0 x ULN
Total bilirubin ↑	umol/L	BILI	5.1 – 20.5 umol/L or 0.3 – 1.2 mg/dL (17.1 x mg/dL = umol/L)	≤ ULN	> ULN - 1.5 x ULN	> 1.5 - 3.0 x ULN	> 3.0 - 10.0 x ULN	> 10.0 x ULN
Alk. Phosphatase ↑	U/L	ALP	36 - 92 U/L or 0.5 - 1.5 ukat/L (60 x ukat/L = U/L)	≤ ULN	> ULN - 2.5 x ULN	> 2.5 - 5.0 x ULN	> 5.0 - 20.0 x ULN	> 20.0 x ULN
Creatinine ↑	umol/L	CREAT	61.9 - 115 umol/L or 0.7 – 1.3 mg/dL (88.4 x mg/dL = umol/L)	≤ ULN	> ULN - 1.5 x ULN	> 1.5 - 3.0 x ULN	> 3.0 - 6.0 x ULN	> 6.0 x ULN
Creatinine kinase ↑	U/L	CK	30 - 170 U/L or 0.5 – 2.83 ukat/L (60 x ukat/L = U/L)	≤ ULN	> ULN - 2.5 x ULN	> 2.5 - 5.0 x ULN	> 5.0 - 10.0 x ULN	> 10.0 x ULN
Albumin (Hypoalbuminemia)	g/L	ALB	35 - 55 g/L or 3.5 to 5.5 g/dL	≥ LLN	< LLN - 30 g/L	< 30 - 20 g/L	< 20 g/L	-
Total Cholesterol ↑	mmol/L	CHOL	3.88 – 5.15 mmol/L or 150 - 199 mg/dL (38.67 x mg/dL = mmol/L)	≤ ULN	> ULN - 7.75 mmol/L > ULN - 300 mg/dL	> 7.75 - 10.34 mmol/L > 300 – 400 mg/dL	> 10.34-12.92 mmol/L > 400 – 500 mg/dL	> 12.92 mmol/L > 500 mg/dL
Lipase ↑	U/L	LIPASE	< 95 U/L or < 1.58 ukat/L (60 x ukat/L = U/L)	≤ ULN	> ULN - 1.5 x ULN	> 1.5 - 2.0 x ULN	> 2.0 - 5.0 x ULN	> 5.0 x ULN
Amylase ↑	U/L	AMYLASE	0 - 130 U/L or 0 – 2.17 ukat/L (60 x ukat/L = U/L)	≤ ULN	> ULN - 1.5 x ULN	> 1.5 - 2.0 x ULN	> 2.0 - 5.0 x ULN	> 5.0 x ULN
Uric acid (Hyperuricemia)	umol/L	URATE	150 - 470 umol/L or 2.5 – 8 mg/dL (59.48 x mg/dL = umol/L)	Defined by clinical criteria only in CTCAE V5				

ULN = Upper Limit of Normal range; LLN = Lower Limit of Normal range

CTC grades for laboratory values in Novartis Oncology (based on CTCAE v5 – Nov 2017)

Page 2

				CTC Grades ⁽¹⁾				
Lab test (toxicity)	SI unit	Lab test (NCDS)	Normal ranges (Merck manual, July 2015) and conversion factors	0	1	2	3	4
Phosphorus (Hypophosphatemia)	mmol/L	PHOS	0.97 – 1.45 mmol/L or 3.0 - 4.5 mg/dL (0.32 x mg/dL = mmol/L)	Defined by clinical criteria only in CTCAE V5				
Calcium (corrected) (Hypercalcemia)	mmol/L	CACALC	2.2 - 2.6 mmol/L or 9 - 10.5 mg/dL (0.2495 x mg/dL = mmol/L)	≤ ULN	> ULN - 11.5 mg/dL > ULN - 2.9 mmol/L	> 11.5 - 12.5 mg/dL > 2.9 - 3.1 mmol/L	> 12.5 - 13.5 mg/dL > 3.1 - 3.4 mmol/L	> 13.5 mg/dL > 3.4 mmol/L
Calcium (corrected) (Hypocalcemia)	mmol/L	CACALC		≥ LLN	< LLN - 8.0 mg/dL < LLN - 2.0 mmol/L	< 8.0 - 7.0 mg/dL < 2.0 - 1.75 mmol/L	< 7.0 - 6.0 mg/dL < 1.75 - 1.5 mmol/L	< 6.0 mg/dL < 1.5 mmol/L
Magnesium (Hypermagnesemia)	mmol/L	MG	0.62 – 0.99 mmol/L or 1.5 – 2.4 mg/dL (0.4114 x mg/dL = mmol/L)	≤ ULN	> ULN - 3.0 mg/dL > ULN - 1.23 mmol/L	-	> 3.0 – 8.0 mg/dL > 1.23 – 3.3 mmol/L	> 8.0 mg/dL > 3.3 mmol/L
Magnesium (Hypomagnesemia)	mmol/L	MG		≥ LLN	< LLN - 1.2 mg/dL < LLN - 0.5 mmol/L	< 1.2 - 0.9 mg/dL < 0.5 - 0.4 mmol/L	< 0.9 - 0.7 mg/dL < 0.4 - 0.3 mmol/L	< 0.7 mg/dL < 0.3 mmol/L
Glucose (non-fasting) (Hyperglycemia)	mmol/L	GLUCSN	<7.8 mmol/L or <140 mg/dL (0.05551 x mg/dL = mmol/L)	Defined by clinical criteria only in CTCAE V5				
Glucose (fasting) (Hyperglycemia)	mmol/L	GLUCSF	3.9 – 5.8 mmol/L or 70 - 105 mg/dL (0.05551 x mg/dL = mmol/L)					
Glucose (Hypoglycemia)	mmol/L	GLUCSN/ GLUCSF		≥ LLN	< LLN - 55 mg/dL < LLN - 3.0 mmol/L	< 55 - 40 mg/dL < 3.0 - 2.2 mmol/L	< 40 - 30 mg/dL < 2.2 - 1.7 mmol/L	< 30 mg/dL < 1.7 mmol/L
Potassium (Hyperkalemia)	mmol/L	K	3.5 - 5.0 mmol/L (0.2558 x mg/dL = mEq/L = mmol/L)	≤ ULN	> ULN - 5.5 mmol/L	> 5.5 - 6.0 mmol/L	> 6.0 - 7.0 mmol/L	> 7.0 mmol/L
Potassium (Hypokalemia)	mmol/L	K		≥ LLN	< LLN - 3.0 mmol/L	-	< 3.0 - 2.5 mmol/L	< 2.5 mmol/L
Sodium (Hypernatremia)	mmol/L	SODIUM	136 - 145 mmol/L (0.435 x mg/dL = mEq/L = mmol/L)	≤ ULN	> ULN - 150 mmol/L	> 150 - 155 mmol/L	> 155 - 160 mmol/L	> 160 mmol/L
Sodium (Hyponatremia)	mmol/L	SODIUM		≥ LLN	< LLN - 130 mmol/L	< 129 - 125 mmol/L	< 124 - 120 mmol/L	< 120 mmol/L
Triglyceride ↑	mmol/L	TRIG	< 2.82 mmol/L or < 250 mg/dL (0.01129 x mg/dL = umol/L)	< 150 < 1.71	≥ 150 - 300 mg/dL ≥ 1.71 – 3.42 mmol/L	> 300 - 500 mg/dL > 3.42 – 5.7 mmol/L	> 500 - 1000 mg/dL > 5.7 – 11.4 mmol/L	> 1000 mg/dL > 11.4 mmol/L
Coagulation								
INR↑	1	INR	0.8 – 1.2	≤ 1.2	> 1.2- 1.5	> 1.5- 2.5	> 2.5	-
Activated partial thromboplastin time↑	sec	APTT	25 - 35 sec	≤ ULN	> ULN - 1.5 x ULN	> 1.5 - 2.5 x ULN	> 2.5 x ULN	-
Fibrinogen ↓	g/L	FIBRINO	1.5 - 3.5 g/L or 150 – 350 mg/dL (0.01 x mg/dL = g/L)	≥ LLN	< LLN - 0.75 x LLN	< 0.75 - 0.5 x LLN	< 0.5 - 0.25 x LLN	< 0.25 x LLN

ULN = Upper Limit of Normal range; LLN = Lower Limit of Normal range

(1) LAB CTC grades 1, 2, 3, 4 overrule the study specific (central or local) normal range criteria, e.g. if ULN of Sodium is 151 mmol/L and the value is 151 mmol/L, CTC grade 2 is assigned although the value is ≥ ULN. Clinical criteria such as 'asymptomatic' or 'Life-threatening consequences' are not considered for determination of LAB CTC grades. Concomitant usage of therapy is also not considered.

Values and LNRs for blood differentials can be given as %, absolute values should then be calculated using WBC. Generally, ≥ 1.5 x 10⁹/L (lymphocytes) and ≥ 2 x 10⁹/L (neutrophils) are considered as LAB CTC grade 0. The comparison with baseline is not considered for derivation of LAB CTC grades.

5.3.1.1 Imputation Rules

CTC grading for blood differentials is based on absolute values. However, this data may not be reported as absolute counts but rather as percentage of WBC.

If laboratory values are provided as '<X' (i.e., below limit of detection) or '>X', prior to conversion of laboratory values to SI unit, then these numeric values are set equal to X.

The following rules will be applied to derive the WBC differential counts when only percentages are available for a xxx differential

$$\text{xxx count} = (\text{WBC count}) * (\text{xxx \% value} / 100)$$

Further derivation of laboratory parameters might be required for CTCAE grading. For instance, corrected calcium can be derived using the reported total calcium value and albumin at the same assessment using the following formula:

$$\text{Corrected Calcium (mg/dL)} = \text{Calcium (mg/dL)} - 0.8 [\text{Albumin (g/dL)} - 4]$$

In order to apply the above formula, albumin values in g/L will be converted to g/dL by multiplying by 0.1, and calcium values in mmol/L will be converted to mg/dL by dividing by 0.2495. For calculation of laboratory CTC grades 0 and 1, the normal range for derived corrected calcium is set to the same limits (in mg/dL) as for calcium.

CTC grades for the derived absolute WBC differential counts (neutrophils, lymphocytes) and corrected calcium will be assigned as described above for grading.

5.4 Derivation of treatment exposure endpoints

5.4.1 Duration of exposure to chemotherapy

Duration of exposure to chemotherapy (days) = (last date of exposure to chemotherapy) – (date of first administration of chemotherapy) + 1.

The last date of exposure to chemotherapy is:

for a drug with daily administration: the date of the last administration of a non-zero dose of the drug

or

for a drug with cyclic administration: the planned end date of the last cycle in which the last non-zero dose of the drug was last administered, or the date of death (if the subject died), or the date of last contact (if the subject was lost to follow-up), or the data cutoff date, whichever is the earliest.

5.4.2 Cumulative dose

Cumulative dose of chemotherapy is defined as the total dose given during the treatment exposure and will be summarized for each of the treatment components.

The **planned cumulative dose** for a chemotherapy refers to the total planned dose as per the protocol.

The **actual cumulative dose** for a chemotherapy refers to the total actual dose administered, over the duration for which the subject is on that treatment as documented in the Dose Administration eCRF.

For subjects who did not take any drug the cumulative dose is by definition equal to zero.

5.4.3 Dose intensity and relative dose intensity

Dose intensity (DI) for subjects with non-zero duration of exposure is defined as follows:

$$\text{DI (dosing unit / unit of time)} = \text{Actual Cumulative dose (dosing unit)} / \text{Duration of exposure to chemotherapy (unit of time)}.$$

For subjects who did not take any drug the DI is by definition equal to zero.

Planned dose intensity (PDI) is defined as follows:

$$\text{PDI (dosing unit / unit of time)} = \text{Planned Cumulative dose (dosing unit)} / \text{Duration of exposure to chemotherapy (unit of time)}.$$

Relative dose intensity (RDI) is defined as follows:

$$\text{RDI} = \text{DI (dosing unit / unit of time)} / \text{PDI (dosing unit / unit of time)}.$$

DI and RDI will be summarized for combination chemotherapy regimens separately for each of the treatment components, but using the duration of exposure of each of the components.

5.4.4 Dose reductions, interruptions or permanent discontinuations for ibrutinib/lenolizumab

The number of subjects who have dose reductions, permanent discontinuations or interruptions, and the reasons, will be summarized separately for each of the treatment components.

‘Dose changed’, ‘Dose interrupted’, and ‘Dose permanently discontinued’ fields from the Dosage Administration CRF pages (DAR) will be used to determine the dose reductions, dose interruptions, and permanent discontinuations, respectively.

The corresponding fields ‘Reason for change’ and ‘Reason for permanent discontinuation’ will be used to summarize the reasons.

A dose change is either ‘change in prescribed dose level’ or ‘dosing error’ where actual dose administered/total daily dose is different from the prescribed dose.

For the purpose of summarizing interruptions and reasons, in case multiple entries for interruption that are entered on consecutive days with different reasons will be counted as separate interruptions. However, if the reason is the same in this mentioned multiple entries on consecutive days, then it will be counted as one interruption.

Reduction: A dose change where the prescribed dose level is lower than the previous prescribed dose level or where the actual dose administered/total daily dose is lower than the calculated dose amount based on the prescribed dose. Therefore any dose change to correct a dosing error will not be considered a dose reduction. Only dose change is collected in the CRF, number of reductions will be derived programmatically based on the change and the direction of the change.

5.5 Statistical models

5.5.1 Analysis of time-to-event data

5.5.1.1 Hypothesis testing

The following one-sided hypothesis will be tested using the stratified log-rank test to address the primary efficacy objectives EFS, and secondary objective OS:

$$H_{01}: \theta \geq 1 \quad \text{vs.} \quad H_{A1}: \theta < 1$$

where θ is the hazard ratio for tisagenlecleucel arm vs. SOC arm.

The stratified log-rank test can be implemented using the example SAS codes attached below

```
proc lifetest data = dataset notable plots=none;
time time * censor(1);
strata str_1 str_2 str 3/ group = trt test=LOGRANK
diff=control('SOC');
run;
```

Please note that the above SAS codes provides the two-sided p-value `pchisq`. The following SAS codes/algorithm may be used to calculate the corresponding one-sided p-value `upchisq`:

```
if estimate < 0 then upchisq = pchisq / 2;
else if estimate > 0 then upchisq = 1 - pchisq / 2;
upchisq = min(1, upchisq);
```

where **estimate** is the coefficient of treatment from PROC PHREG, **pchisq** is the two-sided p-value from PROC LIFETEST, and **upchisq** is the corresponding one-sided p-value.

5.5.1.2 Kaplan-Meier estimates

For time-to-event endpoints (EFS, OS, DOR), an estimate of the survival function in each treatment group will be constructed using the Kaplan-Meier (product-limit) method as implemented in PROC LIFETEST with METHOD=KM option. The PROC LIFETEST statement will use the option CONFTYPE=LOGLOG.

Median survival for each treatment group will be obtained along with 95% confidence intervals calculated from PROC LIFETEST output using the method of [\[Brookmeyer and Crowley 1982\]](#). Kaplan-Meier estimates of the survival function with 95% confidence intervals at specific time points will be summarized. The standard error of the Kaplan-Meier estimate will be calculated using Greenwood's formula [\[Collett 1994\]](#).

5.5.1.3 Hazard ratio

The hazard ratio will be estimated by fitting a Cox proportional hazards model using the SAS procedure PHREG (with TIES=EXACT option in the MODEL statement).

A stratified unadjusted Cox model will be used, i.e. the MODEL statement will include the treatment group variable as the only covariate, and the STRATA statement will include the stratification variables.

The hazard ratio will be presented along with its two-sided 95% confidence interval (based on the Wald test).

In addition, a stratified and covariate adjusted Cox model will also be performed, i.e. the MODEL statement will include the treatment group, and covariates age, gender, race, ECOG performance status at baseline, histological subgroup, stage of disease at study entry and DLBCL subtype, and the STRATA statement will include the stratification variables.

5.5.1.4 Treatment of ties

The STRATA statement in LIFETEST procedure will be used to analyze time to event data with ties. The PHREG procedure in SAS with option TIES=EXACT will be used to fit the Cox proportional hazards model.

5.5.1.5 Checking proportionality of hazard assumption

Plots (SURVIVAL LOGSURV LOGLOGS) generated by the LIFETEST procedure in SAS will be used to provide visual checks of the proportional hazards assumption.

- SURVIVAL plots the estimated survivor functions: the curves should be similar if hazards are proportional
- LOGSURV plots the cumulative hazard functions : the larger cumulative hazard should be a multiple of the smaller cumulative hazards if hazards are proportional
- LOGLOGS plots log (cumulative hazard). The LOGLOG plot will show parallel curves if the hazards are proportional.

5.5.2 Analysis of binary data

ORR will be summarized in terms of percentage rates with 95% CIs. An exact binomial confidence interval (implemented using SAS procedure FREQ with EXACT statement for one-way tables) will be calculated ([Clopper & Pearson, 1934](#)).

SAS procedure FREQ will be used to estimate the proportion of responders (binary outcome =1 or “Yes”), along with the associated 95% ($=100 \times (1 - \text{two-sided } \alpha \text{ level})$) two-sided Pearson-Clopper CI. These estimates are obtained using the following example SAS codes:

```
PROC FREQ DATA = dataset;  
TABLE binary event / binomial(level = "Yes") alpha = two-sided alpha level;  
EXACT binomial;  
RUN;
```

When there are no responders, SAS does not produce a CI by default. To obtain a CI in this situation, PROC FREQ is used as specified above except changing `level="No"`. From the results of this modified procedure, the values in percent of the LCL and UCL of a 0% response rate are calculated as follows:

$$\text{LCL}_{\text{LEVEL}=\text{"Yes"}} (\%) = 100\% - \text{UCL}_{\text{LEVEL}=\text{"No"}} (\%)$$

$$\text{UCL}_{\text{LEVEL}=\text{"Yes"}} (\%) = 100\% - \text{LCL}_{\text{LEVEL}=\text{"No"}} (\%)$$

6 Reference

1. Clopper CJ and Pearson ES (1934). The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrical, 26, 404-413.

2. O'Brien PC and Fleming TR (1979). A multiple testing procedure for clinical trials. *Biometrics*, 35, 549-53.
3. Brookmeyer R and Crowley J (1982). A Confidence Interval for the Median Survival Time. *Biometrics*, 38, 29 - 41.
4. Lan KKG, Demets DL. (1983) Discrete sequential boundaries for clinical trials, *Biometrika*
5. 70, 659-63.
6. Fleming TR, Harrington DP and O'Brien PC (1984). Designs for group sequential tests. *Controlled Clinical Trials*, 5, 348-361.
7. Collet D (1994). *Modelling survival data in medical research*. London, Chapman & Hall.
8. Lee D, Gardner R, Porter DL, et al (2014) Current concepts in the diagnosis and management cytokine release syndrome. *Blood*; 124 (2): 188-195.
9. ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials (2017).
10. Xu Z, Zhen B, Park Y, Zhu B. (2017). Designing therapeutic cancer vaccine trials with delayed treatment effect. *Stat Med*, 36(4): 592-605.

Clinical Development

CTL019/tisagenlecleucel/Kymriah®

CCTL019H2301

**Tisagenlecleucel versus standard of care in adult patients
with relapsed or refractory aggressive B-cell non-Hodgkin
lymphoma: A randomized, open label, phase III trial
(BELINDA)**

Statistical Analysis Plan (SAP)

Document type: SAP Documentation
Document status: Final – Amendment 2
Release date: 09-June-2021
Number of pages: 57

Property of Novartis
For business use only
May not be used, divulged, published or otherwise disclosed
without the consent of Novartis

Document History – Changes compared to previous final version of SAP

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
08-June-2021	Prior to DBL for primary analysis	Additional interim OS analysis added. Updates to planned PRO analyses. Other minor updates added for clarification.	Added an additional interim OS analysis to occur 18 months after the randomization of the last patient. Update to time to definitive deterioration analysis, in order to align analysis with the ICH E9 addendum on estimands. Update removes new-ANP and crossover as censoring reasons to target a treatment policy estimand. Clarification on how to derive censoring date and reason for patients with no baseline assessment for PRO. Added separate analysis of FACT-Lym B-symptoms questions. Clarification on definition of baseline. Assessments on the same day as randomization/infusion can be considered as baseline assessments. Clarification on how to derive the censoring date and reason for EFS for patients who discontinue study prior to week 12 assessment.	Section 1 Section 2.1.1.6 Section 2.4.1.2.3 Section 2.5.3 Section 2.7.2 Section 2.11 Section 2.14
08-Apr-2021	Prior to DBL for primary analysis	Updates due to COVID-19 pandemic (timing of primary analysis and COVID-19 sensitivity analyses) Updates to align SAP with latest protocol amendment version 3	Added clarification on timing of primary analysis that all patients should have week 12 visit (or discontinued early). Added clarification that this SAP is only for analyses of the global study and any analyses of the China extension cohort will be in a separate SAP. Added secondary objective of time to response Added paragraph about subgroup analysis of patients from Japan	Section 1 Section 2.2.6 Section 2.4.2 Section 2.7 Section 2.8.5.3 Section 2.13 Section 5.6

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
			Added clarification that concomitant radiotherapy in a palliative setting is allowed in both arms as part of the treatment strategy	
			Added section to address the secondary objective related to RCL testing	
			Added section to address the exploratory objective related to healthcare resource utilization	
			Added analyses to assess the impact of the COVID-19 pandemic	
			Added time windows for biomarker, immunogenicity, PK and PRO analyses	
			Other minor updates to ensure alignment with protocol	

Table of contents

	Table of contents	4
	List of abbreviations	7
1	Introduction	10
1.1	Study design.....	10
1.2	Study objectives and endpoints	13
2	Statistical methods.....	15
2.1	Data analysis general information	15
2.1.1	General definitions	16
2.2	Analysis sets	18
2.2.1	Screened Set	18
2.2.2	Tisagenlecleucel Infused Set.....	18
2.2.3	Full Analysis Set	19
2.2.4	Safety Set	19
2.2.5	Per-Protocol Set	19
2.2.6	Cellular Kinetic Analysis Set	19
2.2.7	Subgroup of interest	20
2.3	Patient disposition, demographics and other baseline characteristics	21
2.3.1	Subject disposition	21
2.3.2	Analysis Sets	21
2.3.3	Basic demographic and background data.....	21
2.3.4	Medical history.....	22
2.3.5	Diagnosis and extent of cancer	22
2.3.6	Protocol deviations.....	22
2.4	Treatments (study treatment, rescue medication, concomitant therapies, compliance).....	23
2.4.1	Study treatment / compliance.....	23
2.4.2	Prior, concomitant and post therapies	24
2.5	Analysis of the primary objective.....	25
2.5.1	Primary endpoint.....	25
2.5.2	Statistical hypothesis, model, and method of analysis	26
2.5.3	Handling of missing values/censoring/discontinuations.....	26
2.5.4	Supportive analyses.....	27
2.6	Analysis of the key secondary objective	28
2.7	Analysis of secondary efficacy objectives.....	29
2.7.1	Secondary endpoints	29
2.7.2	Statistical hypothesis, model, and method of analysis	30

2.7.3	Handling of missing values/censoring/discontinuations.....	31
2.8	Safety analyses.....	32
2.8.1	Analysis and reporting periods.....	32
2.8.2	Adverse events (AEs).....	33
2.8.3	Deaths.....	36
2.8.4	Laboratory data	36
2.8.5	Other safety data	37
2.9	Cellular kinetics endpoints	37
2.10	Immunogenicity	38
2.10.1	Humoral immunogenicity	39
2.10.2	Cellular immunogenicity.....	39
2.11	Patient-reported outcomes	39
2.12	Biomarkers.....	41
2.12.1	Biomarker data analysis set.....	42
2.12.2	Data handling	42
2.12.3	PD-1 and PD-L1 status and other exhaustion markers	42
2.12.4	Soluble immune factors.....	42
2.13	Other exploratory analyses	42
2.13.1	Healthcare resource utilization.....	42
2.13.2	Impact of COVID-19	43
2.14	Interim analysis.....	43
3	Sample size calculation	43
4	Change to protocol specified analyses	44
5	Appendix	45
5.1	Imputation rules	45
5.1.1	Study drug	45
5.1.2	AE, ConMeds and safety assessment date imputation.....	46
5.1.3	Dates of prior lymphoma, initial diagnosis of cancer, first relapse and most recent recurrence/relapse	47
5.1.4	Response assessments	47
5.1.5	Anti-neoplastic therapies.....	47
5.1.6	Date of hospitalization imputation	48
5.1.7	Incomplete date for death or last known date subject alive	48
5.2	AEs coding/grading	48
5.3	Laboratory parameters derivations	48
5.4	Derivation of treatment exposure endpoints.....	51

5.4.1	Duration of exposure to chemotherapy	51
5.4.2	Cumulative dose	51
5.4.3	Dose intensity and relative dose intensity	51
5.4.4	Dose reductions, interruptions or permanent discontinuations	51
5.5	Statistical models	52
5.5.1	Analysis of time-to-event data	52
5.5.2	Analysis of binary data	53
5.6	Time windows	53
6	Reference	57

List of abbreviations

ABC	Activated B-cell
AE	Adverse event
AESI	Adverse event of special interest
ASTCT	American society for transplantation and cellular therapy
ATC	Anatomical therapeutic chemical
AUC	Area under the curve
Bcl-2	B-cell lymphoma 2
Bcl-6	B-cell lymphoma 6
BEAM	Carmustine, etoposide, cytarabine and melphalan
BIRC	Blinded independent review committee
BOR	Best overall response
CAR	Chimeric antigen receptor
CI	Confidence interval
CK	Cellular kinetic
CKAS	Cellular kinetics analysis set
C _{last}	Last concentration
C _{max}	Maximum concentration
C-myc	C-myc proto-oncogene
CR	Complete response
CRO	Contract research organization
CRP	C-reactive protein
CRS	Cytokine release syndrome
CSF	Cerebral spinal fluid
CSR	Clinical study report
CT	Computerized tomography
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
CV%	Coefficient of variation (%)
DHAP	Cisplatin, cytarabine and dexamethasone
DI	Dose intensity
DLBCL	Diffuse large B-cell lymphoma
DMC	Data monitoring committee
DOR	Duration of response
DRL	Drug reference listing
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
eCRS	Electronic case retrieval strategy
EFS	Event-free survival
EOT	End of treatment
EQ-5D	EuroQol 5 dimension

EQ-VAS	EuroQol visual analogue scale
EWB	Emotional well-being
FACT-G	Functional Assessment of Cancer Therapy – General
FACT-Lym	Functional Assessment of Cancer Therapy – Lymphoma
FAS	Full analysis set
FDG	Fluorodeoxyglucose
FL3B	Follicular lymphoma grade 3B
FWB	Functional well-being
GCB	Germinal center B-cell
HCRU	Health care resource utilization
HDCT	High dose chemotherapy
HR	Hazard ratio
HRQoL	Health related quality of life
HSCT	Hematopoietic stem cell transplant
ICU	Intensive care unit
IL-6	Interleukin 6
IL-10	Interleukin 10
IPI	International prognostic index
IRT	Interactive response technology
ITT	Intention to treat
KM	Kaplan-Meier
LD	Lymphodepleting
LLOQ	Lower limit of quantification
LPLV	Last patient last visit
LYMS	Lymphoma-specific subscale
MCS	Mental component summary
MedDRA	Medical Dictionary for Drug Regulatory Affairs
MRA	Magnetic resonance angiography
NCI	National Cancer Institute
NHL	Non-Hodgkin lymphoma
NGS	Next generation sequencing
NOS	Not otherwise specified
ORR	Overall response rate
OS	Overall survival
PCS	Physical component summary
PD	Progressive disease
PD1	Programmed cell death 1
PET	Positron emission tomography
PFS	Progression-free survival
PK	Pharmacokinetics
PMBCL	Primary mediastinal large B-cell lymphoma
PPS	Per-Protocol Set
PR	Partial response

PRO	Patient-reported outcomes
PWB	Physical well-being
QoL	Quality of life
qPCR	Quantitative polymerase chain reaction
RCL	Replication competent lentivirus
r/r	Relapsed/refractory
R-DHAP	Rituximab plus cisplatin, cytarabine and dexamethasone
R-GDP	Rituximab plus gemcitabine, cisplatin and dexamethasone
R-GemOx	Rituximab plus gemcitabine and oxaliplatin
R-ICE	Rituximab plus ifosfamide, carboplatin, etoposide and mesna
RMST	Restricted mean survival time
SAE	Serious adverse event
SD	Stable disease
SAP	Statistical analysis plan
SF-36 v2	Short Form (36) Health Survey, version 2
SOC	Standard of care
SWB	Social well-being
T _{1/2}	Time to half life
TFLs	Tables, Figures, Listings
TIS	Tisagenlecleucel infused set
T _{last}	Time of last concentration
T _{max}	Time to peak concentration
TOI	Trial outcome index
TS	Total score
UNK	Unknown
VSV-g	Vesicular stomatitis virus/glycoprotein
WBC	White blood cells
WHO	World Health Organization

1 Introduction

This Statistical Analysis Plan (SAP) describes the implementation of the statistical analyses planned in the protocol for study CCTL019H2301: Tisagenlecleucel versus standard of care in adult patients with relapsed or refractory aggressive B-cell non-Hodgkin lymphoma: A randomized, open label, phase III trial (BELINDA).

Up to three clinical study reports (CSRs) could result from this SAP:

- Primary analysis: performed after approximately 200 event-free survival (EFS) events have been documented by the blinded independent review committee (BIRC) and all patients have had their week 12 assessment or discontinued prior to week 12 assessment. If statistically significant, this will trigger the first interim analysis for overall survival (OS).

The timing of the primary analysis was updated compared to the protocol to ensure that all patients have their week 12 assessment (or discontinued early) at the time of primary analysis.

The week 12 assessment is the first assessment for the primary and secondary efficacy objectives and if patients do not have this assessment they would be censored prior to the week twelve assessment or excluded from the analysis.

Due to the COVID-19 pandemic, the study suspended screening and enrollment on 31-Mar-2020. Sites were then reopened on a case-by-case basis starting from 12-May-2020. This resulted in a delay in recruitment for a large number of patients, leading to many patients with a shorter follow-up time than simulated in the original sample size calculations. In particular 30 patients (9.3%) were randomized in 2021. The timing of 200 events confirmed by BIRC is expected to happen in April 2021, meaning that some of these patients might not have yet had their week 12 assessment. The week 12 visit of the last patient randomized is expected in early May 2021.

- Second interim analysis for OS: in case the first interim analysis of OS is not statistically significant, the second interim analysis of OS will be performed approximately 18 months after the last patient was randomized in the global cohort.
- Final analysis: in case the interim analyses of OS are not statistically significant, a final analysis will be performed approximately 5 years after the first patient was randomized.

This SAP is not planned to be used for any other analyses. Other analyses planned to be performed for this study include safety analyses for data monitoring committee (DMC) meetings and an analysis of the China extension cohort. The details of these analyses are contained in separate SAPs.

This SAP was based on version 03 of the study protocol dated 08-January-2021.

1.1 Study design

This is a randomized, open label, multicenter phase III trial comparing the efficacy, safety and tolerability of tisagenlecleucel treatment strategy versus standard of care (SOC) treatment strategy as second line treatment in adult patients with aggressive B-cell non-Hodgkin lymphoma (NHL). Patients must be refractory/relapsed (r/r) within 12 months of last dose of first line immunochemotherapy, which must contain both rituximab and an anthracycline.

Refractory disease is defined as absence of complete response (CR) at the end of first line therapy; relapsed disease is defined as CR at the end of first line therapy followed by progressive disease (PD).

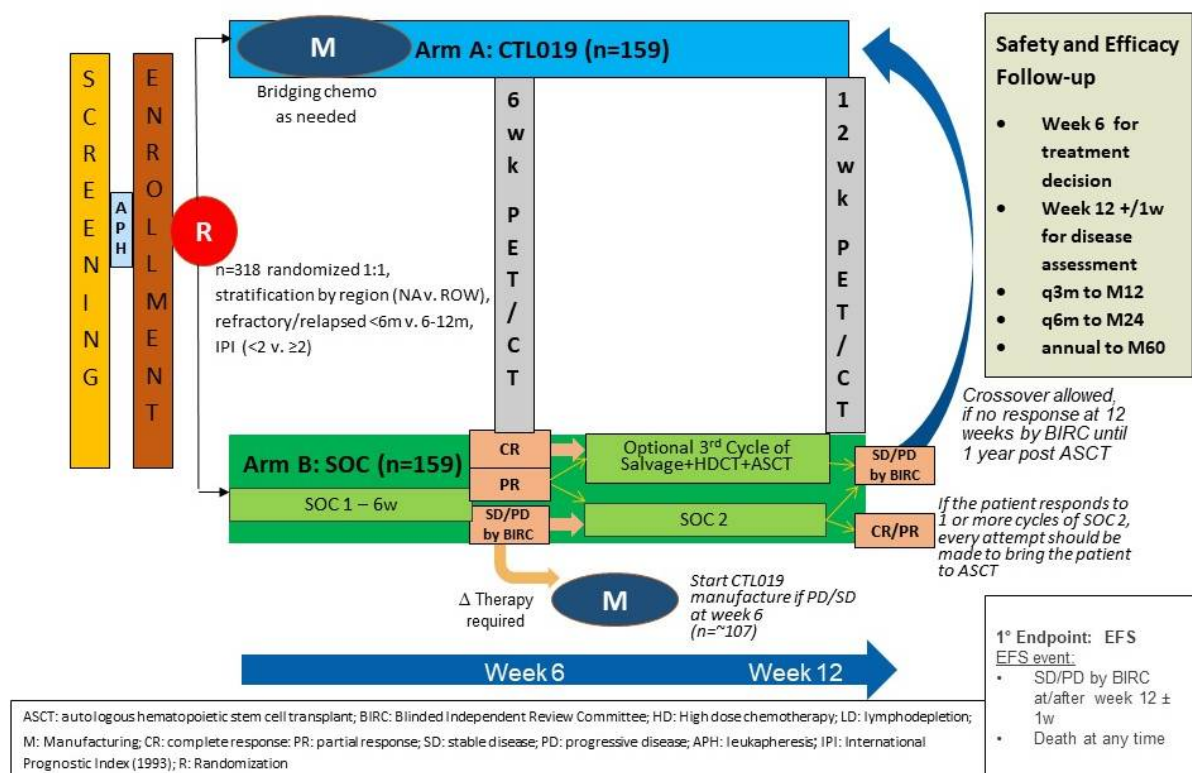
All screened patients will undergo non-mobilized leukapheresis for autologous T cell collection after obtaining informed consent. During the screening period, no lymphoma-specific systemic therapy is allowed prior to randomization.

A subject randomization list has been produced by the Interactive Response Technology (IRT) provider, based on a validated system that automates the random assignment of subject numbers to randomization numbers. Each randomization number is linked to one of the two treatment strategy arms. The randomization is stratified by three binary factors:

- Remission duration: refractory to first line therapy or relapsed < 6 months after last dose of first line therapy versus relapsed 6 - 12 months after last dose of first line therapy
- International Prognostic Index (IPI) score at study entry: < 2 versus ≥ 2
- Region: North America versus Rest of World

The randomization list has been reviewed and approved by a member of the Novartis Randomization Office. The study design is illustrated in [Figure 1-1](#). Eligible patients will be randomized in a 1:1 ratio within each of the eight strata combinations to one of the following arms:

Figure 1-1 Study design



Arm A: tisagenlecleucel treatment strategy, or tisagenlecleucel arm, consisting of optional bridging chemotherapy and lymphodepleting (LD) chemotherapy followed by a single infusion

of tisagenlecleucel. After randomization, tisagenlecleucel is manufactured for the patient, which is expected to take 3-4 weeks. During this period the use of one of four platinum-based bridging immunochemotherapies is allowed (R-ICE, R-DHAP, R-GDP and R-GemOx). Once the tisagenlecleucel product is released by the manufacturing facility, patients should receive LD chemotherapy for 2 or 3 days duration (not required in patients with significant cytopenias), and then receive the tisagenlecleucel infusion about 5 days later. Thus it is expected that tisagenlecleucel infusion will occur approximately 4 to 6 weeks after randomization. Following infusion of tisagenlecleucel, no further anticancer therapies are allowed.

Arm B: standard of care (SOC) treatment strategy, or SOC arm, consisting of standard of care chemotherapy with transplant. Patients will receive one of four platinum-based immunochemotherapies (R-ICE, R-DHAP, R-GDP and R-GemOx) followed in responding patients by high dose chemotherapy (HDCT) and autologous hematopoietic stem cell transplantation (HSCT). Every effort should be made to perform autologous HSCT in patients achieving a PR, if deemed in the patient's best interest by the treating physician. Patients with response that is not sufficient to allow HSCT should change therapy to one of the other immunochemotherapy regimens listed above, at the investigator's discretion in an attempt to achieve a sufficient response and then proceed to HSCT. Only patients who are deemed no longer eligible for HSCT (e.g., due to adverse event [AE], poor tolerance to immunochemotherapy, worsening of performance status) after two cycles of immunochemotherapy may proceed to lenalidomide or ibrutinib treatment at investigator discretion. If the assessment of SD or PD is confirmed by BIRC at the Week 6 assessment, the investigator may request manufacturing of tisagenlecleucel (but not crossover). In addition, patients with PR FDG+ disease, SD or PD per local assessment at the Week 12 assessment may request manufacturing of tisagenlecleucel. Crossover can only occur following confirmation of SD/PD per BIRC at or after the Week 12 assessment, until 1 year after autologous HSCT.

Tumor response assessments will be performed at baseline (within 2 weeks prior to randomization), and post-baseline at the following times after randomization: weeks 6 (± 2 weeks) and 12 (± 1 week), months 6, 9 and 12 (± 2 weeks), months 18 and 24 (± 2 weeks), and thereafter annually (± 2 weeks) until 5 years after randomization. Efficacy will be assessed using the Lugano criteria (as detailed in Appendix 2 of the study protocol).

It is planned to randomize a total of 318 patients. The primary endpoint is EFS, and the primary analysis is to be performed after approximately 200 EFS events have been documented and all patients have had their week 12 assessment or discontinued prior to week 12 assessment. There is no planned interim analysis for EFS, however, an interim analysis for the secondary endpoint of OS will be conducted at the time of the primary analysis, but only if the primary endpoint EFS is statistically significant. If such an interim analysis takes place and OS is not statistically significant, a second interim analysis for OS will be conducted approximately 18 months after the last patient was randomized, and a final analysis for OS will be conducted approximately 5 years after the first patient was randomized.

Note that after recruitment of the 318 patients into the global study, the study will continue enrollment into a China extension cohort. This SAP contains details of the analyses planned for the global study and any patients enrolled into the China extension cohort are excluded from these analyses.

1.2 Study objectives and endpoints

The primary objective of this study is to compare tisagenlecleucel treatment strategy to standard of care (SOC) treatment strategy with respect to EFS.

The two treatment strategies to be compared are defined as:

- Tisagenlecleucel treatment strategy: optional bridging chemotherapy and lymphodepleting chemotherapy followed by a single infusion of tisagenlecleucel
- Standard of Care (SOC) treatment strategy: SOC immunochemotherapy followed in responding patients by high dose chemotherapy (HDCT) and autologous hematopoietic stem cell transplantation (HSCT)

A list of study objectives and related endpoints are provided in Table 1-1, reproduced from the study protocol:

Table 1-1 Objectives and related endpoints

Objectives	Endpoints	Section
Primary Objective		
<ul style="list-style-type: none"> • To compare tisagenlecleucel treatment strategy to SOC treatment strategy with respect to delaying the composite event of disease progression / stable disease at or after the week 12 assessment; or death at any time. 	<ul style="list-style-type: none"> • EFS, defined as time from date of randomization to the date of first documented disease progression or stable disease at or after the week 12 assessment, as assessed by blinded independent review committee (BIRC) per Lugano criteria, or death at any time 	<ul style="list-style-type: none"> • Section 2.5
Secondary Objectives		
<ul style="list-style-type: none"> • To compare tisagenlecleucel treatment strategy to SOC treatment strategy with respect to EFS as assessed by local investigator. 	<ul style="list-style-type: none"> • EFS as assessed by local investigator 	<ul style="list-style-type: none"> • Section 2.5.4
<ul style="list-style-type: none"> • To compare tisagenlecleucel treatment strategy to SOC treatment strategy with respect to overall survival (OS). 	<ul style="list-style-type: none"> • OS: defined as the time from randomization to date of death 	<ul style="list-style-type: none"> • Section 2.7
<ul style="list-style-type: none"> • To compare tisagenlecleucel treatment strategy to SOC treatment strategy with respect to overall response rate (ORR) • To evaluate duration of response (DOR) by BIRC and local investigator. • To compare tisagenlecleucel treatment strategy and SOC treatment strategy with respect to time to response (TTR) 	<p>The following endpoints will be evaluated by BIRC and investigator assessment per Lugano criteria:</p> <ul style="list-style-type: none"> • ORR: overall response rate as per the Lugano criteria • Duration of response: time from the date of first documented response of CR or PR to the date of first documented progression (SD or PD at or after the week 12 assessment will be considered progression) or death due to aggressive B-cell NHL • TTR: time from the date of randomization to the date of a patient first achieved a response of CR or PR on or after the Week 12 assessment 	<ul style="list-style-type: none"> • Section 2.7

<ul style="list-style-type: none"> To evaluate safety and tolerability of tisagenlecleucel treatment strategy versus SOC treatment strategy 	<ul style="list-style-type: none"> Type, frequency and severity of serious and non-serious adverse events and laboratory abnormalities and discontinuations due to adverse events 	<ul style="list-style-type: none"> Section 2.8
<ul style="list-style-type: none"> To compare patient reported outcomes (PRO) of health-related quality of life (HRQoL) in both treatment arms. 	<ul style="list-style-type: none"> Time to definitive deterioration in SF-36v2, FACT-Lym, and EQ-VAS 	<ul style="list-style-type: none"> Section 2.11
<ul style="list-style-type: none"> Evaluate efficacy and safety of both treatment arms in histological subgroups (e.g., DLBCL NOS, FL3B, other) and molecular subgroups (e.g. GCB, ABC, other) 	<ul style="list-style-type: none"> EFS, OS and AE 	<ul style="list-style-type: none"> Section 2.2.6 Section 2.5 Section 2.7
<ul style="list-style-type: none"> To characterize the in vivo cellular kinetics of tisagenlecleucel transduced cells into target tissues (blood, bone marrow, cerebral spinal fluid and other tissues if available), as measured by qPCR summarized by clinical response in patients receiving tisagenlecleucel therapy in arm A or after crossover 	<ul style="list-style-type: none"> Summary of qPCR detected tisagenlecleucel transgene concentrations in peripheral blood and bone marrow (and other tissue, if available), and cellular kinetic parameters from peripheral blood profile samples by time point and clinical response status 	<ul style="list-style-type: none"> Section 2.9
<ul style="list-style-type: none"> To characterize the incidence and prevalence of tisagenlecleucel immunogenicity (humoral and cellular) and impact on cellular kinetics, efficacy, and safety in patients receiving tisagenlecleucel therapy in arm A or after crossover 	<ul style="list-style-type: none"> Summary of pre-existing and treatment induced immunogenicity (cellular and humoral) of tisagenlecleucel Levels of pre-existing and treatment induced immunogenicity. Cellular kinetic parameters, concentration-time profile by immunogenicity category (positive/negative), and efficacy (Month 3 response) 	<ul style="list-style-type: none"> Section 2.10
<ul style="list-style-type: none"> To assess presence of RCL in patients receiving tisagenlecleucel in arm A or after crossover 	<ul style="list-style-type: none"> RCL by VSV-qPCR 	<ul style="list-style-type: none"> Section 2.8.5.3
Exploratory Objectives		
<ul style="list-style-type: none"> Characterize the in vivo cellular kinetics (levels or surface expression) of tisagenlecleucel transduced cells in peripheral blood and to target tissues if available as measured from flow cytometry data, in patients receiving tisagenlecleucel therapy in Arm A or after crossover 	<ul style="list-style-type: none"> Summary of surface expression in peripheral blood, bone marrow as appropriate, by time point 	<ul style="list-style-type: none"> Section 2.9
<ul style="list-style-type: none"> Characterize and summarize cellular kinetics by use of tocilizumab and also by CRS grade in patients receiving tisagenlecleucel therapy in arm A or after crossover 	<ul style="list-style-type: none"> Cmax, Tmax, AUCs, and other cellular kinetic parameters, use of tocilizumab (YES/NO), and CRS grade 	<ul style="list-style-type: none"> Section 2.9
<ul style="list-style-type: none"> To explore the relationship between tisagenlecleucel cellular kinetics, dose, and clinical response (including efficacy and safety) in patients receiving tisagenlecleucel therapy in arm A or after crossover 	<ul style="list-style-type: none"> Parameters: Cmax, Tmax, AUCs, others as appropriate and clinical response parameters (e.g. ORR, DOR, dose) 	<ul style="list-style-type: none"> Section 2.9
<ul style="list-style-type: none"> Explore relationship in baseline tumor biopsy specimens between CD19, PD1 and PD-L1 expression, and clinical response in Arm A or after crossover 	<ul style="list-style-type: none"> ORR, DOR, EFS, CD19 expression, PD-1, PD-L1 expression 	<ul style="list-style-type: none"> Section 2.12.3

<ul style="list-style-type: none"> Profile blood soluble markers (e.g. IL-6, gamma interferon) and their correlation with safety and efficacy in Arm A or after crossover 	<ul style="list-style-type: none"> ORR, DOR, EFS and OS, Concentrations of soluble factors in blood, CRS grade and neuronal toxicity 	<ul style="list-style-type: none"> Section 2.12.4
<ul style="list-style-type: none"> Characterize B cell levels over time in both treatment arms and relationship with transgene persistence, clinical response in patients receiving tisagenlecleucel therapy in arm A or after crossover 	<ul style="list-style-type: none"> B cell levels, cellular kinetics, and clinical response 	<ul style="list-style-type: none"> Section 2.12.5
<ul style="list-style-type: none"> Describe the composition of T cell subsets (immunophenotyping in peripheral blood), summarized by clinical response in Arm A or after crossover 	<ul style="list-style-type: none"> ORR, DOR, EFS and OS, CTL019-positive/CD3-positive/CD4-positive and CTL019-positive/CD3-positive/CD8-positive T cells and other leukocyte subsets 	<ul style="list-style-type: none"> Section 2.12.5
<ul style="list-style-type: none"> Evaluate tisagenlecleucel efficacy in double-hit/triple hit lymphoma patients (Bcl-2, bcl-6 and c-myc expression) in both treatment arms 	<ul style="list-style-type: none"> ORR, DOR, EFS and OS 	<ul style="list-style-type: none"> Section 2.2.6 Section 2.5 Section 2.7
<ul style="list-style-type: none"> To assess health care resource utilization (HCRU) with respect to hospitalization (i.e. length of stay, frequency), outpatient visit (i.e. frequency), and concomitant medication use for selected adverse events (eg, CRS and Neurological events) in both treatment arms 	<ul style="list-style-type: none"> HCRU with respect to hospitalization, outpatient visits, and concomitant medication use for selected adverse events 	<ul style="list-style-type: none"> Section 2.8.2.1.1 Section 2.8.2.1.2 Section 2.13.1

2 Statistical methods

2.1 Data analysis general information

The data will be analyzed by Novartis and/or a designated Contract Research Organization (CRO), including the possible interim analysis of OS (an external statistician is not needed for this interim analysis because it can only be performed after the primary analysis of EFS).

SAS version 9.4 or later, and R version 3.0.2 or later, will be used to perform all data analyses and to generate tables, figures and listings (TFLs).

Data included in the analysis

The primary analysis is the single planned analysis for the primary efficacy endpoint of EFS. A unique data cutoff date will be established after the targeted number of EFS events for the primary analysis (n=200) has been documented by the BIRC and all patients have had a week 12 assessment or discontinued early. All statistical analyses for the primary analysis will be performed using all data collected in the database up to the data cutoff date. All data with an assessment date or event start date (e.g., vital sign assessment date or start date of an AE) prior to or on the cutoff date will be included in the analysis. Any data collected beyond the cutoff date will not be included in the analysis and will not be used for any derivations.

All events with start date before or on the cutoff date and end date after the cutoff date will be reported as 'ongoing'. The same rule will be applied to events starting before or on the cutoff date and not having a documented end date. This approach applies, in particular, to AE and concomitant medication reports. For these cases, the end date will not be imputed and therefore will not appear in the listings.

The data cutoff date for the primary analysis will also serve as the data cutoff date for the first possible interim analysis of the secondary endpoint of OS. The data cutoff date for the second interim analysis of OS will be set at 18 months after the randomization of the last patient. The data cutoff date for the final analysis of OS will be set at 5 years after the randomization of the first patient.

General analysis conventions

Pooling of centers: Unless specified otherwise, data from all study centers will be pooled for the analysis. Due to the expected small number of subjects enrolled at centers, no center effect will be assessed.

Qualitative data (e.g., gender, race, etc.) will be summarized by means of contingency tables by treatment group; a missing category will be included as applicable. Percentages will be calculated using the number of subjects in the relevant population or subgroup as the denominator.

Quantitative data (e.g., age, body weight, etc.) will be summarized by appropriate descriptive statistics (i.e., mean, standard deviation, median, q1, q3, minimum and maximum) by treatment group.

2.1.1 General definitions

2.1.1.1 Treatment strategy

The treatment strategies were defined in [Section 1.2](#) above.

2.1.1.2 Completion of treatment strategy

The tisagenlecleucel treatment strategy is considered completed when the subject is infused with tisagenlecleucel. Subjects are considered as discontinued from the tisagenlecleucel treatment strategy if they discontinue the study without tisagenlecleucel infusion.

The SOC treatment strategy is considered completed when the subject has undergone autologous HSCT following SOC chemotherapy. Subjects are considered as discontinued from the SOC treatment strategy if they discontinue the study or crossover to the tisagenlecleucel arm without autologous HSCT.

2.1.1.3 Start date of treatment strategy

The start date of treatment strategy is defined as the randomization date. The start date of treatment is defined as the first date when a non-zero dose of any component of the treatment strategy was administered.

2.1.1.4 End date of treatment strategy

The end date of treatment strategy is defined as the last date when a non-zero dose of any component of study treatment strategy was administered.

In the case of SOC arm patients who do not go to transplant, and who crossover to tisagenlecleucel, the end date of treatment strategy must be on or before the start date of any

bridging chemotherapy or lymphodepleting chemotherapy administered prior to tisagenlecleucel infusion.

2.1.1.5 Study day

The study day describes the day of an event/assessment relative to the randomization date, and is defined as:

- (date of event/assessment – date of randomization + 1) if event/assessment is on or after the date of randomization
- (date of event/assessment – date of randomization) if event/assessment precedes the date of randomization. In this case the study day will be negative.

The study day will be displayed in the data listings.

In addition, days from tisagenlecleucel infusion will be calculated and listed for selected analyses of efficacy, safety and cellular kinetics post-tisagenlecleucel infusion.

2.1.1.6 Baseline

For **baseline disease evaluations**, the most current assessments (imaging, pathology assessment, bone marrow biopsy or aspirate, CSF cytology, lesions from physical exam findings, etc.) on or prior to the date of randomization will be used as the baseline assessment. (If the assessment is on the date of randomization and assessment time is available, then assessment time must also be before randomization time). Any imaging or disease assessments obtained after randomization cannot be considered for baseline.

For **safety evaluations** (i.e., AEs, laboratory abnormalities, vital signs, etc.), the last available assessment on or prior to the date of randomization is taken as baseline. (If the assessment is on the date of randomization and assessment time is available, then assessment time must also be before randomization time).

In addition, the last available assessment on or before the date of tisagenlecleucel infusion is taken as baseline for selected analyses of efficacy, safety and cellular kinetics post-tisagenlecleucel infusion. (If the assessment is on the date of infusion and assessment time is available, then assessment time must also be before infusion start time).

If patients have no value as defined above, the baseline results will be missing.

In rare cases where multiple measurements meet the baseline definition, with no further flag or label that can identify the chronological order, then the following rule should be applied. If values are from central and local laboratories, the value from central assessment should be considered as baseline.

2.1.1.7 Duration of study follow-up

Duration from the date of randomization until the analysis cutoff date for the primary analysis, or until the LPLV for the final analysis, will be calculated and summarized.

2.1.1.8 Last contact date

The last contact date will be used for censoring of patients in the analysis of OS. For patients not known to have died as of the analysis cutoff date, the last contact date should be derived as the latest date on or before the data cutoff date from the dates listed in the first column of [Table 2-1](#) below. For each of the sources, specific conditions listed in the table have to be fulfilled to ensure that there was true contact with the patient. No additional dates are allowed to be used, for example, dates coming from concomitant medications, PRO, etc.

Table 2-1 Data sources for last contact date

Source data	Conditions
Date of Randomization	No condition
Last date patient was known to be alive from Survival Follow-up page	No condition
Start/End dates from further antineoplastic therapy	Non-missing medication/procedure term
Start/End dates from drug administration record	Non-missing dose
Any specific efficacy assessment date if available	Evaluation is not missing
Laboratory/cellular kinetics collection dates	Sample collection with non-missing value
Vital signs date	At least one non-missing parameter value
Performance Status date	Non-missing performance status
Start/End dates of AE	Non-missing verbatim term

Note: imputed dates will not be used to derive the last contact date with the exception of partially imputed dates from the Survival Follow-up page.

2.1.1.9 Lost to follow-up

For OS analysis, patients will be considered as lost to follow-up if the time between their last contact date and the analysis cutoff date is greater than or equal to 105 days (i.e., 3 months plus 2 weeks, assuming 1 month = 30.4375 days).

For response-related time-to-event analyses (i.e., EFS and DOR), patients will be considered as lost to follow-up only if they discontinued the study due to loss to follow-up.

2.2 Analysis sets

The analysis sets to be used are defined as below.

2.2.1 Screened Set

The screened set comprises all subjects who have signed informed consent and were screened in the study.

2.2.2 Tisagenlecleucel Infused Set

The tisagenlecleucel infused set (TIS) comprises all subjects who received infusion of tisagenlecleucel (i.e., including crossover patients from the SOC arm).

The TIS will be used for all efficacy and safety summaries for subjects infused with tisagenlecleucel. Subjects will be analyzed according to the treatment arm they were originally assigned to during the randomization procedure (i.e. tisagenlecleucel treatment strategy, and crossover from SOC treatment strategy).

2.2.3 Full Analysis Set

The full analysis set (FAS) comprises all subjects to whom study treatment has been assigned by randomization. According to the intent to treat principle, subjects will be analyzed according to the treatment and strata they have been assigned to during the randomization procedure.

The FAS will be used as the main analysis set for efficacy, demographics and other baseline characteristics.

2.2.4 Safety Set

The safety set comprises all subjects to whom study treatment has been assigned by randomization. Subjects will be analyzed according to randomization.

The safety set will be used for all randomized safety comparisons.

2.2.5 Per-Protocol Set

The per-protocol set (PPS) consists of a subset of subjects in the FAS who are compliant with key requirements of the study protocol:

Protocol deviations leading to exclusion from the PPS include:

- Diagnosis of a disease other than histologically confirmed aggressive B-cell NHL (inclusion criterion 3)
- Relapse/progression more than 12 months after last dose of first line therapy for aggressive B-cell NHL (inclusion criterion 4)

2.2.6 Cellular Kinetic Analysis Set

The cellular kinetic analysis set (CKAS) consists of subjects in the tisagenlecleucel infused set (TIS) who provide evaluable tisagenlecleucel cellular kinetic data. A subject is considered as having evaluable cellular kinetic data if at least one cellular kinetic parameter can be derived. The CKAS will be used for summaries (tables and figures) of cellular kinetic data. The TIS will be used for listings of cellular kinetic data.

Note that subjects will be removed from the estimation of certain CK parameters on an individual basis depending on the number of available samples. These subjects will be identified at the time of the analyses.

2.2.7 Subgroup of interest

Efficacy

If the primary efficacy analysis based on the FAS is statistically significant, the primary efficacy endpoint of EFS will be summarized by the following subgroups to examine the homogeneity of the treatment effect:

- Stratification factors, based on the data from eCRF:
 - Remission duration (Refractory or relapsed within 6 months, Relapsed at 6-12 months)
 - IPI at study entry (< 2 , ≥ 2 risk factors)
 - Geographical region (North America, Rest of the World)
- Age (< 65 years, ≥ 65 years)
- Sex (Male, Female)
- Race (Asian, Black or African American, White, Other)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- ECOG performance status (0, 1)
- Elevated LDH (Yes, No)
- Prior response status (Primary refractory, relapsed)
- Histology (e.g., DLBCL NOS, FL3B, PMBCL, High grade B-cell lymphoma, Other)
- Rearrangements in MYC/BCL2/BCL6 genes (Double/Triple hits, Other)
- Stage of disease at study entry (I/II, III/IV)
- Molecular DLBCL cell of origin (Germinal Center B cell [GCB], non-GCB)

No formal statistical test of hypotheses will be performed for the subgroups, only point estimates of the treatment effect and 95%-confidence intervals will be provided. The objective of the efficacy subgroup analysis is to demonstrate homogeneity of treatment effect in the above subgroups. Subgroup analyses will only be performed if adequate number of events are observed.

Safety

Key safety analyses on AESIs, deaths, SAEs and AEs leading to discontinuation will be repeated in the safety set, and in the tisagenlecleucel infused set, in the following subgroups:

- Age (< 65 years, ≥ 65 years)
- Sex (Male, Female)
- Race (Asian, Black or African American, White, Other)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Histology (e.g., DLBCL NOS, FL3B, PMBCL, High grade B-cell lymphoma, Other)
- Molecular: DLBCL cell of origin (GCB, non-GCB)

The objective for carrying out these subgroup analyses is to identify potential safety issues that may be limited to a subgroup of patients, or safety issues that are more commonly observed

in a subgroup of patients. Summary tables will only be performed if at least 5 patients are present in each subgroup. Some grouping of classes will be considered.

In addition, key summary tables and/or figures for efficacy, safety and others will be developed for the Japan subgroup, defined as all patients who have been randomized in the study from the investigational sites located in Japan (i.e., Country = Japan), to address the regulatory submission in Japan. No statistical hypothesis testing will be conducted for the Japan subgroup. Summary tables and/or figures developed for the Japan subgroup will be specified in the TFL shell document.

Note that histology, rearrangements in MYC/BCL2/BCL6 genes and molecular DLBCL cell of origin are reported locally on CRFs, and also tested using central labs. Analyses for the CSR will consistently use locally reported data.

2.3 Patient disposition, demographics and other baseline characteristics

Unless specified otherwise, the FAS will be used for all baseline and demographic summaries. Summaries will be reported by treatment arm and for all subjects. The FAS will also be used for listings, where subjects will be presented by treatment arm.

2.3.1 Subject disposition

Subject disposition will be summarized as follows:

- Screening disposition for the screened set
- Treatment disposition for the FAS by treatment arm
- Study disposition for the FAS by treatment arm

For each disposition, subject status including completed, ongoing or discontinued (with reason for discontinuation) will be summarized based on the number and percentage of subjects as listed on the disposition eCRF pages.

Study follow-up will be summarized numerically as well as by categories: <6 months, 6 months to <12 months, 12 months to <24 months, ≥24 months etc. for the FAS.

All disposition data will be listed using the screened set.

2.3.2 Analysis Sets

The number (%) of subjects in each analysis set (defined in [Section 2.2](#)) will be summarized by treatment group and stratum.

2.3.3 Basic demographic and background data

All demographic and baseline disease characteristics data will be summarized and listed by treatment arm. The following grouping will be applied:

- Age: <65 vs. ≥ 65 years
- ECOG performance status: 0 vs. 1

Baseline stratification factors

The number (%) of subjects in each stratum, based on data obtained from the eCRF, will be summarized overall and by treatment arm for the FAS. Subgroup analysis using descriptive statistics based on stratification factors will also use data from the eCRF. These analyses may be repeated using data from the IRT system, but only if strata membership differs between IRT and eCRF for at least one patient. For statistical models that are stratified by one or more of the baseline stratification factors, the stratification per IRT will be used.

2.3.4 Medical history

Medical history and ongoing conditions, including cancer-related conditions and symptoms entered on eCRF will be summarized by treatment arm.. The summaries will be presented by primary system organ class (SOC), preferred term (PT) and treatment arm. Medical history and current medical conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

2.3.5 Diagnosis and extent of cancer

The summary of diagnosis and extent of cancer (i.e., disease history) will include predominant histological subgroup (e.g., DLBCL NOS, FL3B, PMBCL, etc.), transformation of prior lymphoma, stage at initial diagnosis, stage at time of study entry, lines of therapy for prior lymphoma, lines of therapy for current lymphoma, IPI at study entry, DLBCL cell of origin subtype (local), rearrangements in MYC/BCL2/BCL6 genes (e.g. double/triple hits etc.) (local), time (in months) from initial diagnosis of current lymphoma to start of treatment strategy, time (in months) since most recent relapse/progression to start of treatment strategy, time (in months) from initial diagnosis of current lymphoma to most recent relapse/progression, and time (in months) from diagnosis of prior lymphoma to initial diagnosis of current lymphoma (only for patients with prior lymphoma).

Subjects will be classified by their prior treatment response as:

- Refractory: defined as subjects who did not achieve CR on first line therapy to current lymphoma
- Relapsed: defined as subjects who had CR on first line therapy to current lymphoma and relapsed prior to the study

Note: For subjects who received first line treatment for a prior NHL within the subtypes allowed by the protocol which then transformed into the current lymphoma, remission duration is derived considering the last treatment for the prior lymphoma.

2.3.6 Protocol deviations

The number (%) of subjects in the FAS with any protocol deviation will be tabulated by deviation category (as specified in the study Edit Check document) overall and by treatment group. All protocol deviations will be listed.

2.4 Treatments (study treatment, rescue medication, concomitant therapies, compliance)

2.4.1 Study treatment / compliance

2.4.1.1 Tisagenlecleucel arm

The FAS will be used for all summaries and listings of study treatment.

2.4.1.1.1 Tisagenlecleucel

The total viable cell count (cells) and the total CAR-positive viable T cell count (cells) will be listed and summarized using descriptive statistics. Subjects will be categorized as below, within or above the target dose ranges.

Time from screening and randomization to tisagenlecleucel infusion will be summarized using descriptive statistics.

2.4.1.1.2 Lymphodepleting chemotherapy

The lymphodepleting chemotherapies, received after randomization but prior to tisagenlecleucel infusion will be listed. The number and percentage of subjects who received lymphodepleting chemotherapy will be summarized by therapy type, i.e., fludarabine/cyclophosphamide, bendamustine or other. Duration of exposure ([Section 5.4](#)), actual cumulative dose (in mg/m^2) and reason for therapy discontinuation will also be summarized by therapy type.

2.4.1.1.3 Bridging chemotherapy

Bridging chemotherapies are defined as chemotherapies received after randomization but prior to lymphodepleting chemotherapies. The number and percentage of subjects who received bridging chemotherapy will be summarized by therapy type, i.e., R-ICE, R-DHAP, R-GDP, R-GemOx or other. Duration of exposure ([Section 5.4](#)), dose reduction, interruption or discontinuation and corresponding reasons will also be summarized by therapy type; actual cumulative dose (in mg/m^2) and dose intensity ($\text{mg}/\text{m}^2/\text{day}$) will be summarized by each component of the bridging chemotherapy regimen.

2.4.1.2 SOC arm

2.4.1.2.1 Immunochemotherapy

The number and percentage of subjects who received chemotherapy will be summarized by therapy type, i.e., R-ICE, R-DHAP, R-GDP or R-GemOx. Duration of exposure ([Section 5.4](#)), number of cycles, dose reduction, interruption or discontinuation and corresponding reasons will also be summarized by therapy type; actual cumulative dose (in mg/m^2) and dose intensity ($\text{mg}/\text{m}^2/\text{day}$) will be summarized by each component of the immunochemotherapy regimen.

2.4.1.2.2 Conditioning chemotherapy

The number and percentage of subjects who received conditioning high dose chemotherapy will be summarized by therapy type, i.e., BEAM or other. Duration of exposure ([Section 5.4](#)) and reason for therapy discontinuation will also be summarized by therapy type; actual cumulative dose (in mg/m²) and dose intensity (mg/m²/day) will be summarized by each component of the conditioning chemotherapy.

2.4.1.2.3 Autologous HSCT

The number and percentage of subjects who become ineligible for autologous HSCT during the treatment strategy will be summarized. The reason for ineligibility will also be summarized.

The number and percentage of subjects who underwent autologous HSCT will be summarized.

2.4.2 Prior, concomitant and post therapies

Medications will be coded using the latest version of World Health Organization (WHO) Drug Reference Listing (DRL) dictionary that employs the WHO Anatomical Therapeutic Chemical (ATC) classification system at the time of analysis; surgical and medical procedures will be coded using MedDRA. The versions of the WHO-DRL and the MedDRA that will be used will be footnoted in all relevant outputs.

Prior anti-cancer therapy

Prior anti-cancer therapy refers to all anti-cancer interventions (therapeutic treatments and procedures) for aggressive B-cell NHL that are administered prior to randomization. The number and percentage of subjects in the FAS who received any prior anti-cancer medications, prior anti-cancer radiotherapy or prior anti-cancer surgery will be summarized by treatment arm, and listed separately

New anti-cancer therapy

New anti-cancer therapy consists of anti-cancer therapy administered on or after randomization, excluding therapies given as part of the randomly assigned treatment strategy. As such, new anti-cancer therapy is defined separately for each treatment arm as follows:

In the tisagenlecleucel arm:

- any anti-CD19 or gene therapy other than tisagenlecleucel
- conditioning therapy (high dose chemotherapy) with intention of HSCT
- any anti-neoplastic therapy other than optional bridging chemotherapy (regardless of protocol-specified or not) or lymphodepleting chemotherapy prior to tisagenlecleucel infusion (including for patients who do not go on to receive tisagenlecleucel)
- any anti-neoplastic therapy at any time after tisagenlecleucel infusion

In the SOC arm:

- any anti-CD19 or gene therapy including tisagenlecleucel
- any anti-neoplastic therapy prior to HSCT except SOC treatment options (including patients who do not go to HSCT)

- any anti-neoplastic therapy at any time after HSCT

Please note that in both arms radiation therapy in a palliative setting during the treatment strategy will not be considered as new anti-cancer therapy. Any radiation therapy given after the end of the treatment strategy would be considered a new anti-cancer therapy.

New anti-cancer therapies will be listed and summarized by ATC class, preferred term, overall and by treatment arm by means of frequency counts and percentages using the FAS.

Concomitant therapies

Concomitant therapy is defined as all interventions (therapeutic treatments and procedures) given to a subject during the study other than those specified as study treatment. Concomitant therapy includes medications (other than study drugs) starting on or after randomization or medications starting prior to start date of randomization and continuing after the start date of randomization.

Concomitant medications will be summarized by lowest ATC class and preferred term using frequency counts and percentages by treatment arm. Surgical and medical procedures will be summarized by SOC and preferred term.

All concomitant therapies will be listed. Any concomitant therapies starting and ending prior to the start of study treatment will be flagged in the listing. The FAS will be used for all concomitant medication tables and listings.

Anti-cytokine medications are given for severe CRS due to tisagenlecleucel cells. The number of subjects administered with anti-cytokine medications, type of anti-cytokine medications received, and number of tocilizumab doses given for the management of CRS will be summarized using the TIS.

2.5 Analysis of the primary objective

The primary aim of the study is to compare two second line treatment strategies in adult patients with aggressive B-cell non-Hodgkin lymphoma who are refractory to or relapsed after frontline standard of care and are eligible for stem cell transplantation. The treatment strategies will be compared based on their effect on delaying the composite event of PD / stable disease (SD) at or after the Week 12 assessment or death at any time. These two treatment strategies will be compared based on all randomized patients, irrespective of whether the patient received all or some of the components of the randomized treatment. Intercurrent events preventing compliance with these strategies such as initiation of alternative cancer therapies prior to the composite event of interest, will be handled accordingly. A Cox regression model stratified by randomization stratification factors will be used to estimate the hazard ratio (HR) of EFS.

2.5.1 Primary endpoint

The primary endpoint of the study is EFS, defined as the time from the date of randomization to the date of the first documented PD or SD at or after the Week 12 assessment, as assessed by BIRC per Lugano criteria (see Appendix 2 of the study protocol), or death due to any cause, at any time. The protocol-allowed time window for the Week 12 assessment is +/- 1 week; however, as an analysis convention, response assessments as early as week 10 will be taken into

account as valid Week 12 assessments (i.e., on or after study day 71, where study day 1 is the date of randomization). This approach is taken in case some patients have an early Week 12 assessment, for example to avoid delaying future study treatment options, e.g., HSCT in the SOC arm, tisagenlecleucel infusion in the tisagenlecleucel arm. Censoring conventions are provided in [Section 2.5.3](#).

2.5.2 Statistical hypothesis, model, and method of analysis

The primary efficacy analysis will be the comparison of the distribution of EFS between the two treatment strategies in the FAS. Assuming proportional hazards for EFS, the following statistical hypothesis will be tested to address the primary efficacy objective:

$$H_0: \theta_1 \geq 1 \text{ vs. } H_{A1}: \theta_1 < 1$$

where θ_1 is the EFS HR (tisagenlecleucel arm versus standard-of-care arm). The analysis to test this hypothesis will consist of a stratified log-rank test at an overall one-sided 2.5% level of significance. Stratification will be based on the randomization stratification factors, as assigned in IRT, of remission duration (refractory or relapsed within 6 months vs. relapsed at 6-12 months), IPI score at study entry (< 2 vs. ≥ 2) and region (North America vs. Rest of the World).

There will be no interim analysis for EFS. The final analysis for EFS will be performed on the data observed in the FAS up to the data cutoff date, after approximately 200 EFS events have been documented by the BIRC and all patients have had their week 12 assessment or discontinued prior to week 12 assessment. The study will be considered positive if the stratified log-rank test performed at the final analysis for EFS has a one-sided p-value ≤ 0.025 .

The survival distribution of EFS will be estimated using the Kaplan-Meier (KM) method and will be plotted graphically by treatment arm. The median EFS along with its 95% confidence interval will be presented by treatment arm. The survival probabilities at 3, 6, 9 and 12 months, and the associated 95% confidence intervals, will be summarized by treatment arm. A stratified Cox regression model will be used to estimate the HR of EFS, along with its 95% confidence interval, using the same strata as for the primary efficacy comparison.

2.5.3 Handling of missing values/censoring/discontinuations

The analysis of EFS will be based on all randomized patients, regardless of whether the patient received all or some of the components of the randomized treatment, and the amount of dose received.

If no EFS event is observed prior to the earliest censoring event, EFS will be censored. Censoring events include loss to follow-up, withdrawal of consent, study discontinuation, data cutoff date and initiation of new anticancer therapy (as defined in [Section 2.4.2](#)). If the earliest censoring event occurs before the Week 12 assessment, then EFS will be censored at the date of the censoring event (since only death counts as an EFS event prior to the Week 12 assessment). If the earliest censoring event occurs after the Week 12 assessment, then EFS will be censored at the date of the last assessment with CR/PR prior to the earliest censoring event and on or after the Week 12 assessment. In the case where the Week 12 assessment has a response of “unknown” and the censoring event occurs before any further response assessment with CR/PR, EFS will be censored on the day before the Week 12 assessment. If no assessments

are available after day 70 and before censoring event, EFS will be censored on day 70 (i.e. the last day when only death is considered an event).

2.5.4 Supportive analyses

Patients in the tisagenlecleucel arm are only expected to receive tisagenlecleucel infusion between 4 and 6 weeks after randomization (see [Section 1.1](#)), and before the infusion they may be receiving bridging chemotherapy, consisting of one of the four chemotherapy regimens planned for the SOC arm. As such, any efficacy benefit to the tisagenlecleucel arm is only anticipated to emerge after 4-6 weeks. This delayed treatment effect is an example of non-proportional hazards, and can lead to a loss of power for the stratified log-rank test, the primary analysis in the study. To support the analyses of EFS under non-proportional hazards assumptions, the following supportive analyses will be used to compare EFS per BIRC assessment between the tisagenlecleucel and SOC arms.

2.5.4.1 Weighted log-rank test

Considering the delayed effect of the tisagenlecleucel treatment, piece-wise weighted log-rank test [[Xu et al, 2017](#)]: assigning weights of 0 to event times in the first 6 weeks, and weights of 1 thereafter, in both treatment arms.

The test will be conducted at the one-sided 2.5% level, and be stratified by the randomization stratification factors of remission duration, IPI score at study entry and region. In addition, the treatment effect will be summarized by the average HR and 95% CI obtained from a weighted stratified Cox model, stratified by the randomization stratification factors.

2.5.4.2 Restricted mean survival time

The restricted mean survival time (RMST) [[Zhang, 2013](#)] analysis assesses the treatment difference in expected survival time between two arms with the restriction of a certain cutoff time point (τ). The choice of τ should take into the following considerations: (1) τ should not exceed the minimum of the largest follow-up time for both arms so that the RMST(τ) of both arms can be adequately estimated [[Zhao et al, 2015](#)]; (2) τ should be large enough to cover the majority of patients' outcomes so that the RMST(τ) provides a meaningful assessment of the treatment effect; (3) τ is desired to be clinically meaningful. Given the situation of the patients' enrollment and scheduled assessments, the τ_0 = Month 12 is selected as an appropriate cut-off point. In case the minimum of the largest follow-up time for both arms does not extend beyond Month 12, τ_1 = minimum of largest follow-up time of both arms will be used as the cut-off point.

The RMST (for EFS, by the chosen cutoff point) will be estimated based on the KM method for both tisagenlecleucel arm and SOC arm. RMST will be summarized descriptively by treatment group. The RMST difference between the two arms will be calculated, along with the associated 95% CI.

2.5.4.3 Further supportive analyses

Further supportive analyses will include:

- HR and 95% CI of EFS per BIRC from an unstratified Cox model without any covariate adjustment.

- HR and 95% CI of EFS per BIRC from a stratified Cox model, stratified by the randomization stratification factors of remission duration, IPI at study entry and region, and adjusted for the following possibly prognostic covariates: age, gender, race, ECOG performance status, histological subgroup, stage of disease at study entry and DLBCL subtype.
- EFS per BIRC review in the PPS, using the same analysis method as in the primary efficacy analysis (with the exception of the log rank test, which will not be performed).
- EFS per local investigator review, using the same analyses as in the primary efficacy analysis, with the exception of the log-rank test which will not be performed (this was one of the secondary objectives of the study, see [Section 1.2](#)).

Also depending on the amount of missing assessments, further sensitivity analyses maybe undertaken, for example, censoring EFS after two or more missing response assessments.

If the primary analysis is statistically significant, subgroup analyses to assess the homogeneity of the treatment effect across demographic and baseline disease characteristics will be performed per BIRC. The list of subgroups is provided in [Section 2.2.6](#). The analyses will include KM summaries of median EFS with 95% CI by treatment arm, and stratified Cox models will be used to estimate EFS HR and their 95% CIs. Only subgroups with an adequate number of events (at least 5) will be included. Note that even if the primary analysis is not statistically significant, the above subgroup analyses will be undertaken for both the histological and molecular subgroups, because this is a stated secondary objective of the study (see [Section 1.2](#)).

The number of subjects censored and reasons for censoring will be summarized by treatment arm using descriptive statistics, presented separately for EFS per BIRC and EFS per local investigator review.

Stratified Cox regression models will be repeated for the following alternative definitions of EFS:

1. EFS per BIRC irrespective of new anti-cancer therapy for lymphoma, i.e., EFS events will be counted even if occurring after start of a new anti-cancer therapy. This corresponds to a fully intention-to-treat approach for both treatment strategies
 - This analysis targets the Treatment Policy estimand, i.e. the comparison between tisagenlecleucel treatment strategy and SOC treatment strategy including possible future treatments
2. EFS per BIRC considering new anti-cancer therapy for lymphoma at any time as an EFS event.
 - This analysis considers a Composite estimand, where new anti-cancer therapies are considered the same as PD/SD or death

2.6 Analysis of the key secondary objective

There is no key secondary objective in this study.

2.7 Analysis of secondary efficacy objectives

The secondary efficacy objectives are to compare tisagenlecleucel treatment strategy to SOC treatment strategy with respect to:

- EFS as assessed by local investigator (already discussed in [Section 2.5.4](#) as supportive analysis for primary objective)
- OS
- Overall response rate (ORR), both by BIRC and local investigator assessment
- Duration of response (DOR), both by BIRC and local investigator assessment
- EFS as assessed by BIRC and OS in histological subgroups (DLBCL NOS, FL3B, PMBCL, etc) and molecular subgroups (e.g., GCB, ABC, other)
- Time to response (TTR), both by BIRC and local investigator assessment

2.7.1 Secondary endpoints

Overall survival

OS is defined as the time from date of randomization to date of death due to any cause. A cutoff date will be established for each analysis of OS. All deaths occurring on or before the cutoff date will be used in the OS analysis. If a patient is not known to have died at the data cutoff date, OS will be censored at the date of last contact.

Overall response rate

ORR is defined as the proportion of subjects with best overall response (BOR) of CR or partial response (PR) according to the Lugano criteria (see Appendix 2 of the study protocol for details).

BOR is defined as the best overall disease response from the sequence of overall disease responses, observed between the Week 12 assessment and the first to occur between the data cutoff date, the start date of a new anticancer therapy (as defined in [Section 2.4.2](#)) and the date of EFS event. That is, response assessments before the Week 12 assessment are not used in the calculation of BOR, in order to maintain consistency with the definition of EFS used in this study. For example, a patient with overall disease response of PD at Week 6 followed by CR at Week 12, would have a BOR of CR. Response assessments as early as week 10 (study day 71) will be taken into account as valid Week 12 assessments.

A separate definition “BOR post-infusion” will also be used for PK ([Section 2.9](#)), immunogenicity ([Section 2.10](#)) and biomarker analyses ([Section 2.12](#)) in the tisagenlecleucel infused. This refers to the best overall disease response considering efficacy assessments post-infusion and before the data cutoff date, the start date of a new anticancer therapy and the date of progressive disease).

Duration of response

Duration of response (DOR) only applies to patients whose BOR is CR or PR according to the Lugano criteria. It is defined as the time from the date of first documented response of CR or PR, to the date of the first subsequent documented progression or death due to aggressive B-cell NHL. In this study, “documented progression” refers to a response of SD or PD on or after

the Week 12 assessment, and assessments on or after week 10 (study day 71) will be considered as valid Week 12 assessments. Censoring conventions are provided in [Section 2.7.3](#).

Time to Response

Time to overall disease response (CR or PR) is defined as time from the date of randomization to the date of first documented overall disease response of PR or CR according to Lugano criteria based on disease response data per BIRC on or after the Week 12 assessment.

2.7.2 Statistical hypothesis, model, and method of analysis

Overall survival

OS will only be tested if the primary endpoint (EFS as assessed by BIRC) is statistically significant at the primary analysis for EFS. In that case, and assuming proportional hazards for OS, the following statistical hypotheses will be tested in the FAS:

$$H_{02}: \theta_2 \geq 1 \text{ vs. } H_{A2}: \theta_2 < 1$$

where θ_2 is the OS HR (tisagenlecleucel arm versus standard-of-care arm). The analysis to test this hypothesis will consist of a stratified log-rank test at an overall one-sided 2.5% level of significance. Stratification will be based on the randomization stratification factors: remission duration, IPI score at study entry and region.

If the EFS primary endpoint is statistically significant, OS will be analyzed using a group sequential design with three looks, the first at the time of the primary analysis for EFS, the second 18 months after the randomization of the last patient, and the final look at 5 years after the randomization of the first patient. A Haybittle-Peto boundary will be used, where the one-sided significance level is 0.05% at the two interim analyses and 2.5% at the final analysis. Analyses will be based on the FAS according to the randomized treatment group and stratum assigned at randomization.

Irrespective of whether the EFS primary endpoint is statistically significant or not, the following analyses will be undertaken. The distribution of OS will be estimated using the KM method, and KM curves will be presented. The median OS and the proportion of patients alive at 6 and 12 weeks, and at 6, 12, 18, 24, 36, 48 and 60 months, with 95% confidence intervals, will be presented by treatment arm. The HR for OS will be calculated, along with its 95% confidence interval, using a Cox model stratified by the randomization stratification factors.

Subgroup analyses will be undertaken for histological subtype and molecular subgroup, because these are a stated secondary objective of the study (see [Section 1.2](#)). The analyses will include KM summaries of median OS with 95% CI by treatment arm.

The number of subjects censored for OS and reasons for censoring will be summarized by treatment arm using descriptive statistics.

Overall response rate

ORR based on BIRC assessment will be summarized using descriptive statistics (N, %) by treatment arm, along with two-sided standard Wald asymptotic (i.e., normal approximation) 95% CIs. As a supportive analysis, ORR will also be summarized based on the local investigator

assessment of response data. In addition, comparative summary of BOR between BIRC assessment and local assessment will be provided to evaluate the consistency of the two results.

Furthermore, a descriptive summary of response status at the week 6 assessment will be provided.

Duration of response

DOR will be summarized by treatment arm for all patients in the FAS with BOR of CR or PR. The distribution of DOR will be estimated using the KM method, and KM curves will be presented. The median DOR and the proportion of patients remaining relapse-free at 3, 6, 12, 18, 24, 36, 48 and 60 months after first response, with 95% confidence intervals, will be presented by treatment arm. The HR for DOR will be calculated, along with its 95% confidence interval, using a Cox model stratified by the randomization stratification factors of remission duration, IPI at study entry and region.

Time to response

The TTR analysis will be based on the FAS. TTR will be estimated using the KM method and the median TTR will be presented along with a 95% confidence interval. As a sensitivity analysis, TTR as per investigator assessment will be presented by treatment group, along with 95% confidence intervals.

Descriptive analyses for patients who achieved CR or PR (e.g. mean, SD, median, minimum and maximum) will be presented by treatment group.

2.7.3 Handling of missing values/censoring/discontinuations

Overall survival

If a patient is not known to have died at the data cutoff date, OS will be censored at the date of last contact (see [Section 2.1.1.8](#) for definition of last contact date).

Overall response rate

Patients with unknown or missing BOR will be counted as non-responders. If there is no baseline response assessment, all post-baseline overall disease responses are expected to be Unknown. If no valid post-baseline response assessments are available, the BOR will be Unknown unless progression is reported. For the computation of ORR, these patients will be counted as non-responders.

Duration of response

If no DOR event (i.e., SD/PD on or after the Week 12 assessment or death due to aggressive B-cell NHL) is observed prior to the earliest censoring event, DOR will be censored. The same censoring reasons used in the primary EFS analysis will be used for DOR, with the addition of “death due to reason other than aggressive B-cell NHL”. The censoring date will be the date of the last assessment with response of CR or PR on or prior to the earliest censoring event.

Time to response

TTR will be censored for patients who did not achieve a PR or CR:

- At maximum follow-up (i.e. FPFV to LPLV used for the analysis) for patients who died due to any cause, progressed on or after the week 12 assessment or initiated new anticancer therapy (as defined in [Section 2.4.2](#)),
- At the date of the last adequate assessment on or after the week 12 assessment otherwise.
 - If patient has no adequate assessments on or after the week 12 assessment, patient will be censored at day 1.

2.8 Safety analyses

The main focus of the safety analyses are:

- to compare the safety of the two treatment strategies as defined in [Section 1.2](#) in the safety set (randomized safety comparison)
- to evaluate safety post-tisagenlecleucel infusion in the tisagenlecleucel infused set.

The safety analyses will be based on the analysis sets specified above unless specified otherwise.

2.8.1 Analysis and reporting periods

Note that following the definitions in [Table 2-2](#) below, the **safety comparison period** will be the main safety reporting period for the randomized safety comparison, and the **post-infusion period** will be the main safety reporting period for the evaluation of safety after tisagenlecleucel infusion.

Table 2-2 Safety reporting periods

Period	Definition	Subjects to be included
For both arms		
Screening period *	From the day of subject's informed consent to the day before randomization	Screened set
Safety comparison period	From the day of randomization to the earlier day of starting a new anticancer therapy, or 56 days after last study treatment administration	Safety set
Post safety-comparison period	From the day after the earlier day of starting a new anticancer therapy, or 56 days after last study treatment administration, until end of study	Safety set
For tisagenlecleucel arm and subjects in SOC arm with a crossover visit		
Pre-lymphodepleting period **	From day of randomization (subjects in tisagenlecleucel arm) or day of crossover visit (subjects in SOC arm with a crossover visit) to the day before first lymphodepleting chemotherapy dose or the day before infusion of tisagenlecleucel if lymphodepleting chemotherapy is not given	Full analysis set

Period	Definition	Subjects to be included
Lymphodepleting period ***	From the first day of lymphodepleting chemotherapy to <ul style="list-style-type: none"> the day before infusion of tisagenlecleucel, for subjects who received infusion, or the earlier of date of discontinuation and 30 days after last dose of lymphodepleting chemotherapy for subjects who didn't receive infusion of tisagenlecleucel 	All subjects who received lymphodepleting chemotherapy
Post-infusion period	Starting on the day of the first tisagenlecleucel infusion until end of study	Tisagenlecleucel infused set

* If a subject was not randomized, all the AEs for the subject are considered to be in the screening period.

** If a subject did not receive lymphodepleting chemotherapy or tisagenlecleucel infusion, all the AEs for the subject are considered to be in the pre-lymphodepleting period.

*** This period only applies to subjects who received lymphodepleting chemotherapy.

2.8.2 Adverse events (AEs)

Reporting of AEs follows the modified safety reporting rules described in Protocol Appendix 3.

Reporting of AEs (except for CRS) will be based on MedDRA (latest version per database lock) and the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. The grading of CRS will be primarily based on the Lee criteria [Lee et al, 2014].

- For the randomized safety comparison, AE summaries will include all AEs that started or worsened during the safety comparison period, i.e. **post-randomization** AEs.
- For the safety evaluation post-tisagenlecleucel infusion, AE summaries will include all AEs that started or worsened during the post-infusion period, i.e. **tisagenlecleucel-treatment-emergent** AEs.

AEs will be summarized by number and percentage of subjects with at least one AE, at least one AE in each primary system organ class and for each preferred term. A subject with multiple occurrences of an AE will be counted only once in the respective AE category. A subject with multiple CTCAE grades for the same preferred term will be summarized under the maximum CTCAE grade recorded for the event. AE with missing CTCAE grade will be included in the all grades column of the summary tables. The frequency of AEs of grade 3 or above will be summarized together.

In AE summary tables, the primary system organ class will be presented alphabetically and preferred terms will be sorted within the primary system organ class in descending frequency. The sort order for the preferred terms will be based on their frequency in the 'All grades' column as reported in the tisagenlecleucel arm.

For the **randomized safety comparison**, the following AE summaries will be produced by treatment arm in subjects from the safety set for the safety comparison period:

- Overview of adverse events, deaths, and other serious or clinically significant AEs
- Adverse events, regardless of study treatment relationship, by primary system organ class, preferred term and maximum grade
- Adverse events, suspected to be study treatment related, by primary system organ class, preferred term and maximum grade
- Serious adverse events, regardless of study treatment relationship, by primary system organ class and preferred term and maximum grade
- Serious adverse events, suspected to be study treatment related, by primary system organ class and preferred term and maximum grade
- Adverse events leading to study treatment discontinuation, regardless of study treatment relationship, by primary system organ class and preferred term
- Adverse events leading to study treatment interruption/adjustment, regardless of study treatment relationship, by primary system organ class and preferred term
- Non-serious adverse events, regardless of study treatment relationship, by primary system organ class and preferred term

For the **safety evaluation post-tisagenlecleucel infusion**, the AE summaries listed below will be produced separately for subjects in Arm A and subjects crossed over from Arm B to Arm A from the tisagenlecleucel infused set for the post-infusion period by timing of onset: within 8 weeks of first tisagenlecleucel infusion, >8 weeks to 1 year after the first tisagenlecleucel infusion, >1 year after the first tisagenlecleucel infusion, and any time after the first tisagenlecleucel infusion. The denominator for each time period will be the number of subjects still remaining in the study at the start of the corresponding time period.

- Overview of adverse events, deaths, and other serious or clinically significant AEs
- Adverse events, regardless of tisagenlecleucel relationship, by primary system organ class, preferred term and maximum grade
- Adverse events, suspected to be tisagenlecleucel related, by primary system organ class, preferred term and maximum grade
- Serious adverse events, regardless of tisagenlecleucel relationship, by primary system organ class and preferred term and maximum grade
- Serious adverse events, suspected to be tisagenlecleucel related, by primary system organ class and preferred term and maximum grade
- Non-Serious Adverse events, regardless of tisagenlecleucel relationship, by primary system organ class and preferred term

2.8.2.1 Adverse events of special interest / grouping of AEs

AESIs include all important identified and potential risks of tisagenlecleucel, and may also include additional relevant safety topics (e.g., missing information or exploratory safety topics). The list of AESIs and their search criteria are updated on a regular basis at program level in the electronic Case Retrieval Strategy (eCRS) form. The most recent version of the eCRS form will be used for the reporting activity.

For the **randomized safety comparison**, the AESIs will be summarized by treatment arm in the safety comparison period, in subjects from the safety set.

For the **safety evaluation post-tisagenlecleucel infusion**, AESIs will be summarized separately for subjects in Arm A and subjects crossed over from Arm B to Arm A by drug relationship, group term, preferred term, maximum grade and timing of onset in subjects from the tisagenlecleucel infused set for the post-infusion period by timing of onset: within 8 weeks of first tisagenlecleucel infusion, >8 weeks to 1 year after the first tisagenlecleucel infusion, >1 year after first tisagenlecleucel infusion, and any time after first tisagenlecleucel infusion.

AESI based on important identified risks and potential risks will be summarized in tables by timing of onset:

- AESI post-tisagenlecleucel infusion based on important **identified** risks, regardless of study drug relationship, by group term, preferred term and maximum CTC grade
- AESI post-tisagenlecleucel infusion based on important **potential** risks, regardless of study drug relationship, by group term, preferred term and maximum CTC grade

2.8.2.1.1 Cytokine release syndrome (CRS)

Detailed information regarding the first episode of CRS, including maximum CRS grade, time to onset of CRS, time to resolution of CRS, time to grade 3/4/5 CRS, concurrent infections, timing and duration of ICU stay, selected complications and use of anti-cytokine therapies, will be summarized by treatment arm. Time to resolution of the first CRS episode will be summarized for subjects with CRS using KM methodology. In case the end date of an episode of CRS is missing, it will be censored as the minimum of the cutoff date, end of study evaluation date and death date (if applicable).

Note that CRS grades will be primarily reported according to the Lee criteria [[Lee et al, 2014](#)]. Additionally, CRS will also be assessed using other grading scales (e.g., ASTCT consensus grading) and a sensitivity analysis will be conducted.

2.8.2.1.2 Neurological events

Neurological events refer to a group of neurological AEs defined in the AESI search criteria form. A neurological event episode may include multiple overlapping or consecutive neurological AEs as long as the end date and the start date of two consecutive AEs are no more than 3 days apart (i.e., current AE start date – previous AE end date ≤ 3). The onset day of a neurological event episode is the start date of the first neurological AE in the episode. The resolution date is the end day of the last AE in the episode. If there are multiple AEs with the same last end date and one or more of these AEs are unresolved, the entire episode will be considered unresolved. Time to onset of the first neurological event episode will be summarized descriptively. Time to resolution of all neurological event episodes from all subjects will be summarized using KM methodology, without taking into account that multiple episodes might be clustered by subject. For example, for a subject with two episodes, both episodes will be included in the analysis. Although these two episodes from one subject are not independent, they will be treated as if they are from two subjects (each with one episode).

Neurological events will be reported according to the CTCAE v5.0. Additionally, neurological events will also be assessed using other grading scales (e.g., ASTCT consensus grading) and a sensitivity analysis will be conducted.

2.8.2.1.3 Hematopoietic cytopenias

In addition to the analysis of AEs reported by the investigator, analysis of laboratory results will also be performed for hematopoietic cytopenias not resolved by week 4 (defined as 35 days after the end of study treatment [28 days +7 day window]), ([Section 2.8.4](#)).

2.8.3 Deaths

Summary tables for deaths will be produced by treatment arm, system organ class and preferred term.

For the **randomized safety comparison**, summary tables for deaths will be provided by treatment arm for all deaths occurring in the safety set during the safety comparison period, i.e., from randomization until the earlier date of starting a new anticancer therapy and 56 days after last study treatment administration.

For the **safety evaluation post-tisagenlecleucel infusion**, summary tables for deaths will be provided separately for subjects in Arm A and subjects crossed over from Arm B to Arm A for all deaths in the tisagenlecleucel infused set that occurred after tisagenlecleucel infusion, by timing of death: within 30 days of tisagenlecleucel infusion, >30 days after tisagenlecleucel infusion and any time after tisagenlecleucel infusion.

All deaths will be listed, and study period as defined in [Section 2.8.1](#) will be flagged in the listings.

2.8.4 Laboratory data

For the analysis of laboratory abnormalities, data from central and local laboratories will be combined.

For laboratory tests covered by the CTCAE, Novartis will assign the appropriate CTC grade to each laboratory value. For laboratory tests where grades are not defined by CTCAE, results will be graded by the low/normal/high classification based on laboratory normal ranges.

The following summaries will be produced for hematology and biochemistry laboratory data (by laboratory parameter and treatment arm):

- Shift tables using CTC grades to compare baseline to the worst post-infusion or safety comparison period value
- For laboratory tests where CTC grades are not defined, shift tables using the low/normal/high classification to compare baseline to the worst post-infusion or safety comparison period value.

For the **randomized safety comparison**, the shift tables will be generated for the safety comparison period in subjects from the safety set.

For the **safety evaluation post-tisagenlecleucel infusion**, the shift tables for the tisagenlecleucel arm will be generated separately for subjects in Arm A and subjects crossed over from Arm B to Arm A from the tisagenlecleucel infused set by timing: within 8 weeks of first tisagenlecleucel infusion, >8 weeks to 1 year after first tisagenlecleucel infusion, >1 year after first tisagenlecleucel infusion, and any time after first tisagenlecleucel infusion.

In addition, for the safety evaluation, the percentage of subjects with hematopoietic cytopenia 4 weeks after end of study treatment of grade 3 or above will be summarized. (Note: 4 weeks is defined as 35 days: to allow for visits happening within 7 day time window allowed for visit). Among these subjects, the timing of resolution to grade 2 or below will be presented via KM methodology. The grading of cytopenias will be derived using laboratory results in absolute lymphocytes (hypo), absolute neutrophils (hypo), hemoglobin (hypo), platelet count (hypo) and WBC (hypo) according to CTCAE 5.0. If a subject did not achieve resolution at the last laboratory assessment, timing of resolution will be censored at that time. Patients will also be censored when receiving a new antineoplastic therapy. The KM median time to resolution and estimates of the percentage of unresolved cases at different time points (e.g., month 2, month 3, etc.) will be presented. The analysis will be presented for both the Safety Set and the Tisagenlecleucel Infused Set.

Liver function parameters of interest are total bilirubin (BILI), ALT, AST and alkaline phosphatase (ALP). The number (%) of subjects with worst post-baseline values as per Novartis Liver Toxicity guidelines will be summarized:

- ALT or AST > 3xULN
- ALT or AST > 5xULN
- ALT or AST > 8xULN
- ALT or AST > 10xULN
- ALT or AST > 20xULN
- BILI > 2xULN
- BILI > 3xULN
- ALT or AST > 3xULN & BILI > 2xULN
- ALT or AST > 3xULN & BILI > 2xULN & ALP \geq 2xULN
- ALT or AST > 3xULN & BILI > 2xULN & ALP < 2xULN

2.8.5 Other safety data

2.8.5.1 ECG and cardiac imaging data

All ECG data will be listed by treatment arm, subject and visit, and abnormalities will be flagged.

2.8.5.2 Vital signs

All vital signs data will be listed by treatment group, subject and visit, and if ranges are available, abnormalities will be flagged. Summary statistics will be provided by treatment arm and visit for subjects in the safety set, and by visit for subjects in the tisagenlecleucel infused set.

2.8.5.3 Replication competent lentivirus

The presence of detectable replication competent lentivirus (RCL) will be tested by VSV-G at protocol scheduled assessments and listed.

2.9 Cellular kinetics endpoints

Tisagenlecleucel concentrations in peripheral blood (and bone marrow and CSF if available) will be listed, graphed and summarized (arithmetic and geometric means, standard deviation,

CV%, CV% geometric mean, minimum, median and maximum) by time points, BOR (after infusion) and treatment arm (tisagenlecleucel arm or crossover from SOC arm) for subjects in the cellular kinetic analysis set (CKAS) as assessed by the following:

- Tisagenlecleucel transgene levels as measured by q-PCR
- Tisagenlecleucel transduced cells measured by flow cytometry of CD3-positive/CD4-positive and CD3-positive/CD8-positive tisagenlecleucel transduced cells if feasible.

The cellular kinetics parameters listed in [Table 2-3](#) along with other relevant cellular kinetics parameters will be estimated, if feasible, from the individual concentration versus time profiles using a non-compartmental approach within the modeling program Phoenix[®] (Pharsight, Mountain View, CA) and reported by BOR category. The non-quantifiable concentrations will be imputed to zero for concentration summaries, and will not be included for estimation of cellular kinetics parameters. Results reported but deemed unreliable will be flagged and excluded from the summaries and cellular kinetics parameter derivations.

Table 2-3 Non compartmental cellular kinetics parameters

Parameter	Definition
AUC 0 - 28d and/or AUC0-84d	The AUC from time zero to day 28 and/or day 84 and or other disease assessment days, in peripheral blood (days*copies/ μ g)
C _{max}	The maximum (peak) observed in peripheral blood or other body fluid drug concentration after single dose administration (copies/ μ g)
T _{max}	The time to reach maximum (peak) peripheral blood or other body fluid drug concentration after single dose administration (days)
T _{1/2}	The half-life associated with the elimination phase slope of a semi logarithmic concentration-time curve (days) in peripheral blood
C _{last}	The last observed quantifiable concentration in peripheral blood (copies/ug)
T _{last}	The time of last observed quantifiable concentration in peripheral blood (days)

Descriptive statistics of cellular kinetics parameters (arithmetic and geometric means, standard deviation, CV%, CV% geometric mean, minimum, median and maximum) will be summarized by BOR (after infusion) for subjects in the CKAS. For T_{max} and T_{last} only minimum, median and maximum will be presented. The summary of parameters will be presented separately by Arm A and crossover patients.

For subjects who receive tocilizumab for management of CRS, the cellular kinetic parameters based on qPCR data will be summarized by use of tocilizumab and CRS grades.

2.10 Immunogenicity

The humoral immunogenicity assay measures the antibody titers specific to the tisagenlecleucel molecule prior to and following infusion. Data will be further fractionated to determine proportion of subjects who make transient versus sustained antibody responses. The cellular immunogenicity assay assesses the presence of T lymphocytes activated by the tisagenlecleucel protein. Data will be reported as summary statistics of pre and post-dose levels of activated T lymphocytes.

The analysis of immunogenicity will be performed separately for patients received tisagenlecleucel in Arm A, or patients crossed over from Arm B to Arm A and infused with tisagenlecleucel.

2.10.1 Humoral immunogenicity

The proportion of humoral immunogenicity positive and negative patients will be summarized by time points. Summary statistics will be presented for tisagelecleucel cellular kinetic parameters for qPCR by anti-tisagelecleucel antibody post-infusion status (positive or negative). A strip plot of anti-tisagelecleucel antibodies by time points will be presented. Regarding the boosted/induced humoral immunogenicity, a patient is only defined as positive for tisagelecleucel treatment-induced or -boosted anti-mouse CAR19 (antiCAR19) antibodies when the anti-mCAR19 antibody MFI at any time post-infusion was at least 2.28-fold higher than pre-infusion levels. The summary of cellular kinetic parameters will be presented by categories of patients with and without treated induced boosted/induced anti-CTL019 antibodies.

A scatter plot of baseline anti-tisagelecleucel antibodies versus qPCR AUC0-28d and Cmax will be presented along with the appropriate regression line. In addition boxplots of anti-tisagelecleucel antibodies at enrollment by BOR (after infusion) will be presented. The same response categories will be used for a similar boxplot summarizing the maximum fold change (based on post-infusion/baseline MFI at various time points) of anti-tisagelecleucel post-infusion.

2.10.2 Cellular immunogenicity

All the analyses described in this section will be performed separately for both CD4 and CD8 T cell responses related to both Pool 1 and Pool 2 peptides. The cellular immunogenicity will be summarized by time points and will be presented as strip plots with time points on the x-axis and net responses on y-axis. The strip plot of maximum net response of cellular immunogenicity by BOR (after infusion) will be presented. The scatter plot of maximum net response post baseline versus qPCR AUC0-28d and Cmax will also be presented along with the appropriate regression line. In addition, a summary table will be presented for net response by BOR (after infusion).

2.11 Patient-reported outcomes

Three separate patient-reported outcome (PRO) instruments will be used in the study:

- FACT-Lym: Functional Assessment of Cancer Therapy – Lymphoma, version 4, to assess lymphoma-specific quality of life. It is composed of the FACT-General (FACT-G), a 27-item questionnaire of general questions, and the FACT-Lym lymphoma-specific subscale (FACT-Lym LymS), an additional 15 items that assess patient concerns relating to lymphoma. All questions are scored on a 5-point scale ranging from 0 = “not at all” to 4 = “very much”; negatively worded questions are reverse-scored so that higher scores are always reflective of better health-related quality of life (HRQoL). FACT-G items are divided into four primary domains: PWB (Physical Well-Being; seven items; range, 0–28), SWB (Social Well-Being; seven items; range, 0–28), EWB (Emotional Well-Being; six items; range, 0–24), and FWB (Functional Well-Being; seven items; range, 0–28). The FACT-Lym LymS consists of common lymphoma disease and/or treatment-related symptoms (e.g., pain, fever, swelling, night sweats, insomnia, itching, weight loss, fatigue and loss of appetite). Three summary scales: FACT-Lym TOI (Trial Outcome Index; range, 0–116; composed of the PWB, FWB, FACT-Lym LymS); FACT-G (range, 0–108;

composed of the PWB, FWB, SWB, EWB), and the FACT-Lym TS (Total Score; range, 0–168; composed of all of the scales) are also calculated.

- EQ-5D-5L: EuroQol 5D, to assess health utility for the purpose of economic evaluation. It is composed of the EQ-VAS, a visual analogue scale from 0-100 with higher values indicating better HRQoL, and the EQ-5D assessing five dimensions of health state (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) on an ordinal scale with five categories: “no”, “slight”, “moderate”, “severe” and “extreme”.
- SF-36v2: Short Form (36) Health Survey, version 2, to assess general health and quality of life. It is composed of 36 questions making 8 domains (physical functioning, role – physical, bodily pain, general health, vitality, social functioning, role – emotional, mental health), from which two overall component scores are obtained: PCS (Physical Component Summary) and MCS (Mental Component Summary). Domain and component summary scores are converted to norm-based scores based on the general population, with higher scores indicative of better HRQoL. The scoring of the questionnaire will be provided by the vendor for this instrument.

For missing items within any questionnaire, prorated scores will be calculated according to developer guidance.

All summary scores from the FACT-Lym, the EQ-VAS and the SF-36v2 will be tabulated for each treatment arm in the FAS, presented over time by scheduled visit. Change from baseline in the scores at the time of each assessment will also be summarized, where baseline is defined as the last PRO assessment on or prior to randomization.

The individual scores and change from baseline for B-symptoms from the FACT-Lym over time by scheduled visit will also be summarized separately. The three B-symptom questions are: bothered by fevers (FACTLY31), night sweats (FACTLY32), and losing weight (FACTLY36).

For each of the five dimensions of the EQ-5D-5L, the proportions of patients in each treatment arm in the FAS having reported “no”, “slight”, “moderate”, “severe” and “extreme” problems will be tabulated at each time-point.

Change from baseline item scores means and 95% CIs will be plotted by visit and by treatment arm.

Time to definitive deterioration

A secondary objective of the study is to compare the treatment arms with respect to the PRO scores. The FACT-Lym TOI will be the primary score for this objective. In addition, the FACT-Lym LymS, FACT-Lym TS and FACT-G will be analyzed as secondary scores, as will the EQ-VAS from the EQ-5D-5L, and the PCS and MCS from the SF-36v2. Note that treatment comparisons based on hypothesis tests will be considered as descriptive only, and no adjustment for multiple testing will be performed.

The primary PRO endpoint will be time to definitive deterioration, defined as the time from randomization to the date of definitive deterioration. For FACT-Lym TOI, a clinically meaningful deterioration is defined as a decrease from baseline of at least 5.5 points, and the decrease is considered definitive if there is no later improvement above this threshold. The date

of definitive deterioration is the earliest such post-baseline assessment. In the absence of an earlier definitive deterioration, patients are censored at the date of the last assessment before the data cutoff date. Patients with no baseline data will be censored at day 1, due to no baseline assessment.

Death is considered as a definitive deterioration when it occurs within a period of time defined by twice the period between two assessments as planned in the study protocol. This avoids overestimating the time to definitive worsening in patients dying after an irregular assessment scheme. Patients who die after more than twice the planned period between two assessments since the last assessment are censored at the date of their last available questionnaire. For patients with no baseline assessment, death is considered as definitive deterioration if the death happens on or before study day 85 (twice the planned assessment period of 42 days), otherwise patient is censored on day 1 due to no baseline assessment.

Time to definitive deterioration in the FACT-Lym TOI will be compared between the two treatment arms in the FAS using a stratified log-rank test at the one-sided 2.5% level of significance. The test will be stratified by the randomization stratification factors of remission duration, IPI score at study entry and region, as assigned at randomization in IRT. The survival distributions will be presented descriptively using KM curves.

Similar analyses of time to definitive deterioration will be performed on the secondary PRO scales of interest as listed above, with deterioration defined as a decrease from baseline of ≥ 2.9 points for FACT-Lym LymS, ≥ 6.5 points for FACT-Lym TS, ≥ 3 points for FACT-G, ≥ 7 points for EQ-VAS, and ≥ 3 points for both PCS and MCS. Sensitivity analysis may be conducted for PCS and MCS using ≥ 5 as the MCID.

A supportive analysis of time to first deterioration may also be conducted, because of the possibility that first deterioration is not definitive due to crossover and new anti-neoplastic therapies.

2.12 Biomarkers

As a project standard, Novartis Oncology Biostatistics and Data Management will analyze only biomarkers collected in the clinical database. Studies are often not adequately powered to assess specific biomarker-related hypotheses, and for this reason the exploratory biomarker analyses that will be undertaken should be considered as promoting the generation of new scientific hypotheses or observing new trends. These hypotheses may be compared with results found in the literature, as well as verified with data derived from subsequent clinical trials. No adjustment for multiple comparisons is usually planned for exploratory analyses. Additional post hoc exploratory assessments are expected and may be performed.

Additional analysis may be performed after the completion of the end-of-study CSR and will be documented in separate reports. These analyses may include, but are not limited to, the meta-analysis of data from this study combined with data from other studies, or the analysis of biomarkers generated from samples collected during the study but analyzed after database lock and completion of the CSR. The data analysis will be described in an addendum of the SAP or in a stand-alone analysis plan document, as appropriate.

There may be circumstances when a decision is made to stop sample collection, or not perform or discontinue the analysis due to either practical or strategic reasons (e.g., issues related to the

quality and/or quantity of the samples, or issues related to the assay). Under such circumstances, the number of samples may be inadequate to perform a rigorous data analysis and the available data will only be listed and potentially summarized.

2.12.1 Biomarker data analysis set

The Full Analysis Set will be used for all biomarker analysis. Unless otherwise specified, all statistical analyses of biomarker data will be performed on patients with biomarker data.

2.12.2 Data handling

Serum cytokine values below the lower limit of quantitation (which may be reported with the label Lower Limit of Quantification [LLOQ]) or have a numerical value below the assay's lower limit of quantitation) will be imputed / replaced as $0.5 \times \text{LLOQ}$, which will be specified by the performing laboratory and is assay- and analyte-specific. In cases when an actual value below LLOQ is reported, this value should not be used and the data should be imputed as $0.5 \times \text{LLOQ}$.

2.12.3 PD-1 and PD-L1 status and other exhaustion markers

CD19 expression in tumor biopsy specimens at baseline, PD-1 and PD-L1 expression levels and their interaction score if available will be summarized for Arm A and crossover patients by BOR (after infusion).

2.12.4 Soluble immune factors

The profile of blood soluble proteins and inflammatory cytokines and receptors (IL-10, interferon gamma, IL-6, CRP, and ferritin) will be summarized by time point and BOR (after infusion) for Arm A and crossover patients with longitudinal plots of mean time-profiles. Fold change from baseline will also be calculated for each time point and displayed with longitudinal plots. If both the baseline and post baseline values are below Lower Limit of Quantification (LLOQ), fold change from baseline will not be imputed and reported as missing. B cell and T cell characterization

The levels of blood B and/or T cells will be summarized by time point and treatment arm for all enrolled patients using longitudinal plots. Only data up to the time of new antineoplastic therapy will be considered (as defined in [Section 2.4.2](#)).

T cell subsets by immunophenotyping will be explored in relation to efficacy endpoints for Arm A and crossover patients if data is available. Patient level and average longitudinal plots of the cell counts and fold changes from baseline may be generated by BOR (after infusion).

2.13 Other exploratory analyses

2.13.1 Healthcare resource utilization

Descriptive statistics of hospitalizations, including total number and duration of hospitalizations, and total duration of ICU stay will be provided by treatment group for the safety set during the safety comparison period.

2.13.2 Impact of COVID-19

Additional analyses may be performed to assess the impact that the COVID-19 pandemic had on the conduct of the trial. Patient disposition ([Section 2.3.1](#)), demographics ([Section 2.3.3](#)), diagnosis and extent of cancer ([Section 2.3.5](#)), and study treatments ([Section 2.4.1](#)) will be summarized by pandemic period and treatment group.

Pandemic period is defined as:

1. During the pre-pandemic period
2. During the pandemic period

The pandemic period is defined to have started on 01-Jan-2020 in China, 21-Feb-2020 in Japan, 23-Feb-2020 in Italy and on 01-Mar-2020 in the rest of the world.

For patient disposition, demographics, and diagnosis and extent of cancer, patients will be included in the respective pandemic period group based on their country and randomization date (or screen failure date for screen failure patients).

For study treatments, patients will be included in the respective pandemic period group based on their country and study treatment completion/discontinuation date.

Note that no end date of the pandemic period has been defined yet and therefore there is no “post-pandemic period” group

Protocol deviations ([Section 2.3.6](#)) and their relationship to the COVID-19 pandemic will be summarized by treatment group.

The impact of COVID-19 on the study conduct will be assessed based on these analyses and based on these results further sensitivity analyses of efficacy and safety data may be considered.

2.14 Interim analysis

No interim analysis is planned for this trial for the primary endpoint of EFS. A hierarchical testing procedure will be adopted and the statistical test for OS will be performed only if the primary efficacy endpoint, EFS is statistically significant.

Three analyses are planned for OS: 1) an interim analysis at the time of the primary analysis for EFS (provided EFS is significant, as outlined in [Section 2.7.2](#)) in the FAS, 2) a second interim analysis 18 months after the randomization of the last patient, and 3) a final analysis for OS at approximately 5 years from the first patient randomized. A Haybittle–Peto boundary will be used for testing OS, where the one-sided significance level is 0.05% at the two interim analyses and 2.5% at the final analysis.

3 Sample size calculation

Based on the data from the ORCHARRD study (Novartis unpublished analyses), EFS time for patients who were randomized to receive salvage chemotherapy (DHAP plus Rituximab or DHAP plus Ofatumumab), who never reached CR before or relapsed within 12 months from response to previous therapy, or had a response of PR, SD or PD to previous therapy was considered as a reference for SOC. In ORCHARRD study, for these patients, who continue to be in SD status at the end of cycle 2/3 (which is earlier than the 12 week assessment, each cycle:

21 days) or had progressed earlier than the 12 week assessment, based on the definition of EFS endpoint used in BELINDA (where documented SD/PD at the Week 12 assessment is considered an EFS event), EFS event time was adjusted to 12 weeks, to account for these earlier events.

The 9 month EFS rate is estimated to be 22.32% in SOC arm and is assumed to be 40% in tisagenlecleucel arm. Due to delayed tisagenlecleucel infusion of 6 weeks and ignoring SD/PD at week 6, we assume piecewise HR in both treatment arms. The HR between two arms during the first 6 weeks is assumed to be 1 and 0.61 after 6 weeks. Given those assumptions, a total of 200 EFS events are required to have 92% power at an one-sided 2.5% level of significance to reject the null hypothesis (i.e. the survival functions for EFS in the two arms are identical), using a stratified log-rank test with equal weights. The sample size calculation was conducted via simulation with software package East 6.4.

Based on a recruitment period of approximately 21 months using staggered enrollment rates of 2, 10, and 16 patients in the 1st 3 months followed by 17 patients thereafter, and assuming 15% drop out rate, a total of approximately 318 patients will need to be randomized to the two treatment arms in a 1:1 ratio. Given the above assumptions, it is estimated that the 200th EFS event will be observed at approximately 23 months from the date of first patient randomized.

4 Change to protocol specified analyses

1. In [Section 2.4.2](#), definition of new anti-cancer therapy for SOC arm: protocol specified that:
 - any anti-neoplastic therapy prior to HSCT except protocol-allowed-SOC treatment options (including patients who do not go to HSCT).

After discussion with the clinical team, it was decided that SOC treatments even if not protocol allowed, if taken prior to HSCT or for those who do not go to HSCT but are still eligible, is a protocol deviation but should not be considered as new anti-cancer therapy. Accordingly, the following updates have been made in the SAP:

- any anti-neoplastic therapy prior to HSCT except SOC treatment options (including patients who do not go to HSCT but are still eligible)
2. Added an efficacy subgroup analysis based on ECOG performance status (0, 1) and Elevated LDH (Yes, No).
 3. Added analyses to assess the impact of COVID-19.
 4. Section 12.6.1 of the protocol specifies that efficacy and PRO would also be summarized after tisagenlecleucel infusion for crossover patients from SOC arm as an exploratory analysis. However, this is not an objective/endpoint of the study ([Section 1.2](#)) and will not be analyzed in the CSR.
 5. A secondary endpoint of the study is time to definitive deterioration in SF-36v2, FACT-Lym and EQ-VAS. Further PRO analyses described in the protocol, e.g. mixed-effects models and improvement rates, will be performed outside the CSR, because they are not endpoints of the study.

6. An extra interim analysis of OS has been added to occur 18 months after the randomization of the last patient. The testing strategy using a Haybittle-Peto boundary remains unchanged and the additional interim analysis does not affect either of the original two planned looks.

5 Appendix

5.1 Imputation rules

5.1.1 Study drug

The following rule should be used for the imputation of the dose end date for a given study treatment component:

Scenario 1: If the dose end date is completely missing and there is no EOT page and no death date, the subject is considered as on-going:

The subject should be treated as on-going and the cutoff date should be used as the dose end date.

Scenario 2: If the dose end date is completely or partially missing and the EOT page is available:

Case 1: The dose end date is completely missing, and the EOT completion date is complete, then this latter date should be used.

Case 2: Only Year(yyyy) of the dose end date is available and $yyyy < \text{the year of EOT date}$:

Use Dec31yyyy

Case 3: Only Year(yyyy) of the dose end date is available and $yyyy = \text{the year of EOT date}$:

Use EOT date

Case 4: Both Year(yyyy) and Month (mm) are available for dose end date, and $yyyy = \text{the year of EOT date}$ and $mm < \text{the month of EOT date}$:

Use last day of the Month (mm)

All other cases should be considered as a data issue and the statistician should contact the data manager of the study.

After imputation, compare the imputed date with start date of treatment, if the imputed date is < start date of treatment:

Use the treatment start date

Subjects with missing start dates are to be considered missing for all study treatment component related calculations and no imputation will be made. If start date is missing then end-date should not be imputed.

5.1.2 AE, ConMeds and safety assessment date imputation

Table 5-1 Imputation of start dates (AE, CM) and assessments (LB, EG, VS)

Missing Element	Rule
day, month, and year	<ul style="list-style-type: none"> No imputation will be done for completely missing dates
day, month	<ul style="list-style-type: none"> If available year = year of study treatment start date then <ul style="list-style-type: none"> If stop date contains a full date and stop date is earlier than study treatment start date then set start date = 01JanYYYY Else set start date = study treatment start date. If available year > year of study treatment start date then 01JanYYYY If available year < year of study treatment start date then 01JulYYYY
day	<ul style="list-style-type: none"> If available month and year = month and year of study treatment start date then <ul style="list-style-type: none"> If stop date contains a full date and stop date is earlier than study treatment start date then set start date= 01MONYYYYY. Else set start date = study treatment start date. If available month and year > month and year of study treatment start date then 01MONYYYYY If available month and year < month year of study treatment start date then 15MONYYYYY

Table 5-2 Imputation of end dates (AE)

Missing Element	Rule
day, month, and year	<ul style="list-style-type: none"> Completely missing end dates (incl. ongoing events) or with end date on or after the cutoff date will be imputed by min(cutoff date, end of study evaluation, date of death, withdrawal of consent date)
day, month	<ul style="list-style-type: none"> If partial end date contains year only, set end date = min(31DEC, cutoff date, end of study evaluation, date of death, withdrawal of consent date)
day	<ul style="list-style-type: none"> If partial end date contains month and year, set end date = min(last day of the month, cutoff date, end of study evaluation, date of death, withdrawal of consent date)

Partial or missing ConMeds end dates will not be imputed.

Any AEs and ConMeds with partial/missing dates will be displayed as such in the data listings.

Any AEs and ConMeds which are continuing as per data cutoff will be shown as ‘ongoing’ rather than the end date provided.

Note that if the imputed AE start date is after the AE end date (regardless of if the end date is imputed or not), use the AE end date as the imputed AE start date.

5.1.3 Dates of prior lymphoma, initial diagnosis of cancer, first relapse and most recent recurrence/relapse

If the day or month of prior lymphoma, initial diagnosis, first relapse or most recent relapse is missing, it will be imputed to the minimum of the informed consent date -1 and the following:

- Missing day: 15th day of the month and year
- Missing day and month: July 1st of the year

5.1.4 Response assessments

All investigation dates for response (e.g., dates of PET scan, CT scan, bone marrow biopsy) must be completed with day, month and year. At any response assessment, if one or more investigation dates are incomplete, the response assessment date is calculated from the complete investigation dates as follows: if the overall disease response at that assessment is CR/PR/SD/UNK, then the assessment date is assigned as the latest complete investigation date, otherwise if overall disease response is PD, then the assessment date is the earliest complete investigation date at that assessment. If no investigation dates at a particular response assessment have day recorded, the 1st of the month is used. If month is not recorded at any of the investigations at a particular response assessment, the response assessment date will be imputed to the mid-point between the previous and following assessments. If a previous and following assessment are not available, this response assessment will not be used for any calculation.

5.1.5 Anti-neoplastic therapies

5.1.5.1 Prior therapies

Start date:

The same rule which is applied to the imputation of AE/concomitant medication start date will be used with the exception that for scenario (B) will be replaced to be 'randomization date -1'.

End date:

Imputed date = min (randomization date, last day of the month), if day is missing;

Imputed date = min (randomization date, 31DEC), if month and day are missing.

If the end date is not missing and the imputed start date is after the end date, use the end date as the imputed start date.

If both the start date and the end date are imputed and if the imputed start date is after the imputed end date, use the imputed end date as the imputation for the start date.

5.1.5.2 Post therapies

Start date:

Imputed date = max (randomization date + 1, first day of the month), if day is missing;

Imputed date = max (randomization date + 1, 01JAN), if day and month are missing.

End date: No imputation.

5.1.6 Date of hospitalization imputation

Missing hospitalization end date or end date after data cutoff will be imputed following the same conventions as for AE end date imputation.

5.1.7 Incomplete date for death or last known date subject alive

If the day or month of death is missing from the death CRF, death will be imputed to the maximum of the full (non-imputed) last contact date ([Section 2.1.1.8](#)) and the following:

- Missing day: 15th day of the month and year of death
- Missing day and month: July 1st of the year of death

If the day or month of last known date subject alive is missing in the survival CRF, it will be first imputed with the following:

- Missing day: minimum of the date of assessment and 15th day of the month and year of last known date subject alive
- Missing day and month: minimum of the date of assessment and July 1st of the year of last known date subject alive

Then the above imputed last known date subject alive will be used to calculate the last contact date as defined in [Section 2.1.1.8](#).

5.2 AEs coding/grading

AEs are coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

AEs will be assessed according to CTCAE version 5.0, except for CRS, where grading of CRS will be primarily based on the Lee criteria [[Lee et al, 2014](#)]

The CTCAE represents a comprehensive grading system for reporting the acute and late effects of cancer treatments. CTCAE grading is by definition a 5-point scale generally corresponding to mild, moderate, severe, life threatening and death. This grading system inherently places a value on the importance of an event, although there is not necessarily proportionality among grades (a grade 2 is not necessarily twice as bad as a grade 1).

5.3 Laboratory parameters derivations

Grade categorization of laboratory values will be assigned programmatically as per NCI CTCAE version 5.0. The calculation of CTCAE grades will be based on the observed laboratory values only, clinical assessments will not be taken into account. The criteria to assign CTCAE grades are given in Novartis internal criteria for CTCAE grading of laboratory parameters per [Table 5-3](#).

For laboratory tests where grades are not defined by CTCAE version 5.0, results will be graded by the low/normal/high (or other project-specific ranges, if more suitable) classifications based on laboratory normal ranges.

A severity grade of 0 will be assigned for all non-missing laboratory values not graded as 1 or higher. Grade 5 will not be used. For laboratory tests that are graded for both low and high

values, summaries will be done separately and labelled by direction, e.g., sodium will be summarized as hyponatremia and hypernatremia.

Table 5-3 CTC grades for laboratory values based on CTCAE v5

CTC grades for laboratory values in Novartis Oncology (based on CTCAE v5 – Nov 2017)

Page 1

				CTC Grades ⁽¹⁾				
Lab test (toxicity)	SI unit	Lab test (NCDS)	Normal ranges (Merck manual, July 2015) and conversion factors	0	1	2	3	4
Hematology								
WBC ↓ WBC (Leukocytosis)	10 ⁹ /L 10 ⁹ /L	WBC WBC	3.9 – 10.7 x 10 ⁹ /L	≥ LLN	< LLN - 3.0 x 10 ⁹ /L -	< 3.0 – 2.0 x 10 ⁹ /L -	< 2.0 – 1.0 x 10 ⁹ /L > 100 x 10 ⁹ /L	< 1.0 x 10 ⁹ /L -
Hemoglobin (Anemia) Hemoglobin ↓	g/L g/L	HGB HGB	120 - 160 g/L or 7.4 - 9.9 mmol/L (F) 140 - 170 g/L or 8.7 – 10.6 mmol/L (M) (16.113 x mmol/L = g/L)	≥ LLN	< LLN - 100 g/L < LLN - 6.2 mmol/L Increase >0-20 g/L above ULN	< 100 - 80 g/L < 6.2 - 4.9 mmol/L Increase >20-40 g/L above ULN	< 80 g/L < 4.9 mmol/L Increase >40 g/L above ULN	- - -
Platelets ↓	10 ⁹ /L	PLAT	150 - 350 x 10 ⁹ /L	≥ LLN	< LLN - 75.0 x 10 ⁹ /L	< 75.0 - 50.0 x 10 ⁹ /L	< 50.0 - 25.0 x 10 ⁹ /L	< 25.0 x 10 ⁹ /L
Neutrophils ↓	10 ⁹ /L	NEUT		≥2x10 ⁹ /L	< 2.0 - 1.5 x 10 ⁹ /L	< 1.5 - 1.0 x 10 ⁹ /L	< 1.0 - 0.5 x 10 ⁹ /L	< 0.5 x 10 ⁹ /L
Lymphocytes ↓ Lymphocytes ↑	10 ⁹ /L 10 ⁹ /L	LYM LYM		≥1.5x10 ⁹ /L	< 1.5 - 0.8 x 10 ⁹ /L -	< 0.8 - 0.5 x 10 ⁹ /L > 4 - 20 x 10 ⁹ /L	< 0.5 - 0.2 x 10 ⁹ /L > 20 x 10 ⁹ /L	< 0.2 x 10 ⁹ /L -
Biochemistry								
AST ↑	U/L	AST	0 - 35 U/L or 0 – 0.58 ukat/L (60 x ukat/L = U/L)	≤ ULN	> ULN – 3.0 x ULN	> 3.0 - 5.0 x ULN	> 5.0 - 20.0 x ULN	> 20.0 x ULN
ALT ↑	U/L	ALT	0 - 35 U/L or 0 – 0.58 ukat/L (60 x ukat/L = U/L)	≤ ULN	> ULN – 3.0 x ULN	> 3.0 - 5.0 x ULN	> 5.0 - 20.0 x ULN	> 20.0 x ULN
Total bilirubin ↑	umol/L	BILI	5.1 – 20.5 umol/L or 0.3 – 1.2 mg/dL (17.1 x mg/dL = umol/L)	≤ ULN	> ULN - 1.5 x ULN	> 1.5 - 3.0 x ULN	> 3.0 - 10.0 x ULN	> 10.0 x ULN
Alk. Phosphatase ↑	U/L	ALP	36 - 92 U/L or 0.5 - 1.5 ukat/L (60 x ukat/L = U/L)	≤ ULN	> ULN - 2.5 x ULN	> 2.5 - 5.0 x ULN	> 5.0 - 20.0 x ULN	> 20.0 x ULN
Creatinine ↑	umol/L	CREAT	61.9 - 115 umol/L or 0.7 – 1.3 mg/dL (88.4 x mg/dL = umol/L)	≤ ULN	> ULN - 1.5 x ULN	> 1.5 - 3.0 x ULN	> 3.0 - 6.0 x ULN	> 6.0 x ULN
Creatinine kinase ↑	U/L	CK	30 - 170 U/L or 0.5 – 2.83 ukat/L (60 x ukat/L = U/L)	≤ ULN	> ULN - 2.5 x ULN	> 2.5 - 5.0 x ULN	> 5.0 - 10.0 x ULN	> 10.0 x ULN
Albumin (Hypoalbuminemia)	g/L	ALB	35 - 55 g/L or 3.5 to 5.5 g/dL	≥ LLN	< LLN - 30 g/L	< 30 - 20 g/L	< 20 g/L	-
Total Cholesterol ↑	mmol/L	CHOL	3.88 – 5.15 mmol/L or 150 - 199 mg/dL (38.67 x mg/dL = mmol/L)	≤ ULN	> ULN - 7.75 mmol/L > ULN - 300 mg/dL	> 7.75 - 10.34 mmol/L > 300 – 400 mg/dL	> 10.34-12.92 mmol/L > 400 – 500 mg/dL	> 12.92 mmol/L > 500 mg/dL
Lipase ↑	U/L	LIPASE	<95 U/L or <1.58 ukat/L (60 x ukat/L = U/L)	≤ ULN	> ULN - 1.5 x ULN	> 1.5 - 2.0 x ULN	> 2.0 - 5.0 x ULN	> 5.0 x ULN
Amylase ↑	U/L	AMYLASE	0 - 130 U/L or 0 – 2.17 ukat/L (60 x ukat/L = U/L)	≤ ULN	> ULN - 1.5 x ULN	> 1.5 - 2.0 x ULN	> 2.0 - 5.0 x ULN	> 5.0 x ULN
Uric acid (Hyperuricemia)	umol/L	URATE	150 - 470 umol/L or 2.5 – 8 mg/dL (59.48 x mg/dL = umol/L)	Defined by clinical criteria only in CTCAE V5				

ULN = Upper Limit of Normal range; LLN = Lower Limit of Normal range

CTC grades for laboratory values in Novartis Oncology (based on CTCAE v5 – Nov 2017)

Page 2

CTC Grades ⁽¹⁾								
Lab test (toxicity)	SI unit	Lab test (NCDS)	Normal ranges (Merck manual, July 2015) and conversion factors	0	1	2	3	4
Phosphorus (Hypophosphatemia)	mmol/L	PHOS	0.97 – 1.45 mmol/L or 3.0 – 4.5 mg/dL (0.32 x mg/dL = mmol/L)	Defined by clinical criteria only in CTCAE V5				
Calcium (corrected) (Hypercalcemia)	mmol/L	CACALC	2.2 – 2.6 mmol/L or 9 – 10.5 mg/dL (0.2495 x mg/dL = mmol/L)	≤ ULN	> ULN - 11.5 mg/dL > ULN - 2.9 mmol/L	> 11.5 – 12.5 mg/dL > 2.9 – 3.1 mmol/L	> 12.5 – 13.5 mg/dL > 3.1 – 3.4 mmol/L	> 13.5 mg/dL > 3.4 mmol/L
Calcium (corrected) (Hypocalcemia)	mmol/L	CACALC		≥ LLN	< LLN - 8.0 mg/dL < LLN - 2.0 mmol/L	< 8.0 – 7.0 mg/dL < 1.75 – 1.5 mmol/L	< 7.0 – 6.0 mg/dL < 1.75 – 1.5 mmol/L	< 6.0 mg/dL < 1.5 mmol/L
Magnesium (Hypomagnesemia)	mmol/L	MG	0.62 – 0.99 mmol/L or 1.5 – 2.4 mg/dL (0.4114 x mg/dL = mmol/L)	≤ ULN	> ULN - 3.0 mg/dL > ULN - 1.23 mmol/L	-	> 3.0 – 8.0 mg/dL > 1.23 – 3.3 mmol/L	> 8.0 mg/dL > 3.3 mmol/L
Magnesium (Hypomagnesemia)	mmol/L	MG		≥ LLN	< LLN - 1.2 mg/dL < LLN - 0.5 mmol/L	< 1.2 – 0.9 mg/dL < 0.5 – 0.4 mmol/L	< 0.9 – 0.7 mg/dL < 0.4 – 0.3 mmol/L	< 0.7 mg/dL < 0.3 mmol/L
Glucose (non-fasting) (Hyperglycemia)	mmol/L	GLUCSN	<7.8 mmol/L or <140 mg/dL (0.05551 x mg/dL = mmol/L)	Defined by clinical criteria only in CTCAE V5				
Glucose (fasting) (Hyperglycemia)	mmol/L	GLUCSF	3.9 – 5.8 mmol/L or 70 – 105 mg/dL (0.05551 x mg/dL = mmol/L)					
Glucose (Hypoglycemia)	mmol/L	GLUCSN/ GLUCSF		≥ LLN	< LLN - 55 mg/dL < LLN - 3.0 mmol/L	< 55 - 40 mg/dL < 3.0 - 2.2 mmol/L	< 40 - 30 mg/dL < 2.2 - 1.7 mmol/L	< 30 mg/dL < 1.7 mmol/L
Potassium (Hyperkalemia)	mmol/L	K	3.5 – 5.0 mmol/L (0.2558 x mg/dL = mmol/L)	≤ ULN	> ULN - 5.5 mmol/L	> 5.5 - 6.0 mmol/L	> 6.0 - 7.0 mmol/L	> 7.0 mmol/L
Potassium (Hypokalemia)	mmol/L	K		≥ LLN	< LLN - 3.0 mmol/L	-	< 3.0 - 2.5 mmol/L	< 2.5 mmol/L
Sodium (Hypernatremia)	mmol/L	SODIUM	136 – 145 mmol/L (0.435 x mg/dL = mmol/L)	≤ ULN	> ULN - 150 mmol/L	> 150 - 155 mmol/L	> 155 - 160 mmol/L	> 160 mmol/L
Sodium (Hyponatremia)	mmol/L	SODIUM		≥ LLN	< LLN - 130 mmol/L	< 129 - 125 mmol/L	< 124 - 120 mmol/L	< 120 mmol/L
Triglyceride †	mmol/L	TRIG	< 2.82 mmol/L or < 250 mg/dL (0.01129 x mg/dL = mmol/L)	< 150 < 1.71	≥ 150 - 300 mg/dL ≥ 1.71 – 3.42 mmol/L	> 300 - 500 mg/dL > 3.42 – 5.7 mmol/L	> 500 - 1000 mg/dL > 5.7 – 11.4 mmol/L	> 1000 mg/dL > 11.4 mmol/L
Coagulation								
INR†	†	INR	0.8 – 1.2	≤ 1.2	> 1.2 - 1.5	> 1.5 - 2.5	> 2.5	-
Activated partial thromboplastin time†	sec	APTT	25 - 35 sec	≤ ULN	> ULN - 1.5 x ULN	> 1.5 - 2.5 x ULN	> 2.5 x ULN	-
Fibrinogen ‡	g/L	FIBRINO	1.5 – 3.5 g/L or 150 – 350 mg/dL (0.01 x mg/dL = g/L)	≥ LLN	< LLN - 0.75 x LLN	< 0.75 - 0.5 x LLN	< 0.5 - 0.25 x LLN	< 0.25 x LLN

ULN = Upper Limit of Normal range; LLN = Lower Limit of Normal range

(1) LAB CTC grades 1, 2, 3, 4 overrule the study specific (central or local) normal range criteria, e.g. if ULN of Sodium is 151 mmol/L and the value is 151 mmol/L, CTC grade 2 is assigned although the value is ≥ ULN. Clinical criteria such as 'asymptomatic' or 'life-threatening consequences' are not considered for determination of LAB CTC grades. Concomitant usage of therapy is also not considered.

Values and LNRs for blood differentials can be given as %, absolute values should then be calculated using WBC. Generally, ≥ 1.5 x 10⁹/L (lymphocytes) and ≥ 2 x 10⁹/L (neutrophils) are considered as LAB CTC grade 0. The comparison with baseline is not considered for derivation of LAB CTC grades

5.3.1.1 Imputation Rules

CTC grading for blood differentials is based on absolute values. However, this data may not be reported as absolute counts but rather as percentage of WBC.

If laboratory values are provided as '<X' (i.e., below limit of detection) or '>X', prior to conversion of laboratory values to SI unit, then these numeric values are set equal to X.

The following rules will be applied to derive the WBC differential counts when only percentages are available for a xxx differential

$$\text{xxx count} = (\text{WBC count}) * (\text{xxx \% value} / 100)$$

Further derivation of laboratory parameters might be required for CTCAE grading. For instance, corrected calcium can be derived using the reported total calcium value and albumin at the same assessment using the following formula:

$$\text{Corrected Calcium (mg/dL)} = \text{Calcium (mg/dL)} - 0.8 [\text{Albumin (g/dL)} - 4]$$

In order to apply the above formula, albumin values in g/L will be converted to g/dL by multiplying by 0.1, and calcium values in mmol/L will be converted to mg/dL by dividing by 0.2495. For calculation of laboratory CTC grades 0 and 1, the normal range for derived corrected calcium is set to the same limits (in mg/dL) as for calcium.

CTC grades for the derived absolute WBC differential counts (neutrophils, lymphocytes) and corrected calcium will be assigned as described above for grading.

5.4 Derivation of treatment exposure endpoints

5.4.1 Duration of exposure to chemotherapy

Duration of exposure to chemotherapy (days) = (last date of exposure to chemotherapy) – (date of first administration of chemotherapy) + 1.

The last date of exposure to chemotherapy is the date of the last administration of a non-zero dose of the drug.

5.4.2 Cumulative dose

Cumulative dose of chemotherapy is defined as the total dose given during the treatment exposure and will be summarized for each of the treatment components.

The **actual cumulative dose** for a chemotherapy refers to the total actual dose administered, over the duration for which the subject is on that treatment.

For subjects who did not take any drug the cumulative dose is by definition equal to zero.

5.4.3 Dose intensity and relative dose intensity

Dose intensity (DI) for subjects with non-zero duration of exposure is defined as follows:

$$DI \text{ (dosing unit / unit of time)} = \text{Actual Cumulative dose (dosing unit)} / \text{Duration of exposure to chemotherapy (unit of time)}.$$

For subjects who did not take any drug the DI is by definition equal to zero.

DI will be summarized for combination chemotherapy regimens separately for each of the treatment components, but using the duration of exposure of each of the components.

5.4.4 Dose reductions, interruptions or permanent discontinuations

The number of subjects who have dose reductions, permanent discontinuations or interruptions, and the reasons, will be summarized separately for each of the treatment components.

‘Dose changed’, ‘Dose interrupted’, and ‘Dose permanently discontinued’ fields from the Study treatment chemotherapy CRF pages will be used to determine the dose reductions, dose interruptions, and permanent discontinuations, respectively.

The corresponding field ‘Reason for change/interruption/discontinued’ will be used to summarize the reasons.

For the purpose of summarizing interruptions and reasons, in case multiple entries for interruption that are entered on consecutive days with different reasons will be counted as separate interruptions. However, if the reason is the same in this mentioned multiple entries on consecutive days, then it will be counted as one interruption.

Reduction: A dose change where the prescribed dose level is lower than the previous prescribed dose level or where the actual dose administered/total daily dose is lower than the calculated dose amount based on the prescribed dose. Therefore any dose change to correct a dosing error will not be considered a dose reduction. Only dose change is collected in the CRF, number of reductions will be derived programmatically based on the change and the direction of the change.

5.5 Statistical models

5.5.1 Analysis of time-to-event data

5.5.1.1 Hypothesis testing

The following one-sided hypothesis will be tested using the stratified log-rank test to address the primary efficacy objectives EFS, and secondary objective OS:

$$H_{01}: \theta \geq 1 \quad \text{vs.} \quad H_{A1}: \theta < 1$$

where θ is the HR for tisagenlecleucel arm vs. SOC arm.

The stratified log-rank test can be implemented using the example SAS codes attached below

```
proc lifetest data = dataset notable plots=none;
time time * censor(1);
strata str_1 str_2 str 3/ group = trt test=LOGRANK
diff=control('SOC');
run;
```

Please note that the above SAS codes provides the two-sided p-value `pchisq`. The following SAS codes/algorithm may be used to calculate the corresponding one-sided p-value `upchisq`:

```
if estimate < 0 then upchisq = pchisq / 2;
else if estimate > 0 then upchisq = 1 - pchisq / 2;
upchisq = min(1, upchisq);
```

where **estimate** is the coefficient of treatment from PROC PHREG, **pchisq** is the two-sided p-value from PROC LIFETEST, and **upchisq** is the corresponding one-sided p-value.

5.5.1.2 Kaplan-Meier estimates

For time-to-event endpoints (EFS, OS, DOR), an estimate of the survival function in each treatment group will be constructed using the KM (product-limit) method as implemented in PROC LIFETEST with METHOD=KM option. The PROC LIFETEST statement will use the option CONFTYPE=LOGLOG.

Median survival for each treatment group will be obtained along with 95% confidence intervals calculated from PROC LIFETEST output using the method of [Brookmeyer and Crowley, 1982]. KM estimates of the survival function with 95% confidence intervals at specific time points will be summarized. The standard error of the KM estimate will be calculated using Greenwood's formula [Collett, 1994].

5.5.1.3 Hazard ratio

The HR will be estimated by fitting a Cox proportional hazards model using the SAS procedure PHREG (with TIES=EXACT option in the MODEL statement).

A stratified unadjusted Cox model will be used, i.e. the MODEL statement will include the treatment group variable as the only covariate, and the STRATA statement will include the stratification variables.

The HR will be presented along with its two-sided 95% confidence interval (based on the Wald test).

In addition, a stratified and covariate adjusted Cox model will also be performed, i.e. the MODEL statement will include the treatment group, and covariates age, gender, race, ECOG performance status at baseline, histological subgroup, stage of disease at study entry and DLBCL subtype, and the STRATA statement will include the stratification variables.

5.5.1.4 Treatment of ties

The STRATA statement in LIFETEST procedure will be used to analyze time to event data with ties. The PHREG procedure in SAS with option TIES=EXACT will be used to fit the Cox proportional hazards model.

5.5.1.5 Checking proportionality of hazard assumption

Plots (SURVIVAL LOGSURV LOGLOGS) generated by the LIFETEST procedure in SAS will be used to provide visual checks of the proportional hazards assumption.

- SURVIVAL plots the estimated survivor functions: the curves should be similar if hazards are proportional
- LOGSURV plots the cumulative hazard functions : the larger cumulative hazard should be a multiple of the smaller cumulative hazards if hazards are proportional
- LOGLOGS plots log (cumulative hazard). The LOGLOG plot will show parallel curves if the hazards are proportional.

5.5.2 Analysis of binary data

ORR will be summarized in terms of percentage rates with 95% CIs. An exact binomial confidence interval (implemented using SAS procedure FREQ with EXACT statement for one-way tables) will be calculated [[Clopper & Pearson, 1934](#)].

SAS procedure FREQ will be used to estimate the proportion of responders (binary outcome =1 or “Yes”), along with the associated 95% ($=100 \times (1 - \text{two-sided } \alpha \text{ level})$) two-sided Pearson-Clopper CI. These estimates are obtained using the following example SAS codes:

```
PROC FREQ DATA = dataset;
TABLE binary event / binomial(level = "Yes") alpha = two-sided alpha level;
EXACT binomial;
RUN;
```

When there are no responders, SAS does not produce a CI by default. To obtain a CI in this situation, PROC FREQ is used as specified above except changing **level="No"**. From the results of this modified procedure, the values in percent of the LCL and UCL of a 0% response rate are calculated as follows:

$LCL_{LEVEL="Yes"} (\%) = 100\% - UCL_{LEVEL="No"} (\%)$

$UCL_{LEVEL="Yes"} (\%) = 100\% - LCL_{LEVEL="No"} (\%)$

5.6 Time windows

In order to summarize biomarker, immunogenicity, PK, and PRO data over time, assessments will be time-slotted using the following time windows. These windows will be based on the study evaluation schedule and should comprise a set of days around the nominal visits. As a

general rule, the following steps are followed to determine the cutoffs for post-baseline time windows:

- Transform all scheduled assessment time points into study days, assuming 1 month = 30.4375 days. Middle points of scheduled assessments are determined.
- The time window associated with the previous assessment ends prior to the middle point; the time window associated with the latter assessment begins after the middle point. In case the middle point is an exact study day, it will belong to the previous assessment.
- The time window of first post-baseline assessment starts with Day 2, unless otherwise indicated.

If more than one assessment is done within the Baseline time window, the last assessment in the baseline time window will be used. For all other time windows, the assessment closest to the planned assessment date will be used; if two or more assessments are equidistant from the planned date, then the mean value will be used.

For each analysis, baseline is either defined as the most recent sample/assessment prior to randomization or the most recent sample/assessment prior to tisagenlecleucel infusion. Visit timing and time window definitions can similarly be defined either based on study day (i.e. from randomization) or on days since tisagenlecleucel infusion.

Table 5-4 shows the defined time windows for biomarker samples for analyses based on the FAS with timings based on randomization date.

Table 5-4 Time windows for biomarker analyses based on full analysis set

Time Window	Planned visit timing (study day)	Time Window Definition (Study day)
B cell, T cell and NK cell characterization		
D1 Randomization	1	≤ Study Day 1
Week 12 ±7d	84	2 to 133
M6 ±14d	183	134 to 274
M12 ±14d	365	275 to 456
M18 ±14d	548	457 to 639
M24 ±14d	731	640 to 913
M36 ±14d	1096	914 to 1278
M48 ±14d	1461	1279 to 1643
M60 ±14d	1826	≥ 1644
Study Day 1 = randomization date		

Table 5-5 shows the defined time windows for biomarker samples for analyses based on the TIS with timings based on infusion date.

Table 5-5 Time windows for biomarker analyses based on tisagenlecleucel infused set

Time Window	Planned visit timing (infusion day)	Time Window Definition (Infusion day)
Serum cytokine and soluble immune factors		
Infusion -7d to infusion -3d ¹	Before infusion day -1	< first day of LD chemotherapy
Infusion -1d ²	-1	Day of LD chemotherapy to day 1 pre-infusion

Infusion +1d	2	Day 1 post-infusion to 3
Infusion +3d ±1d	4	4 to 5
Infusion +6d ±1d	7	6 to 9
Infusion +10d ±3d	11	10 to 12
Infusion +13d ±3d	14	13 to 18
Infusion +21d ±3d	22	19 to 25
Infusion +28d ±7d	29	26 to 35
Week 12 ±7d ³	42	36 to 91
M6 ±14d ³	141	92 to 232
M12 ±14d ³	323	≥ 233
B cell, T cell and NK cell characterization		
Infusion -7d to infusion -3d ¹	Before infusion day -1	< first day of LD chemotherapy
Infusion -1d ²	-1	Day of LD chemotherapy to day 1 pre-infusion
Infusion +6d ±1d	7	Day 1 post infusion to 9
Infusion +10d ±3d	11	10 to 12
Infusion +13d ±3d	14	13 to 28
Week 12 ±7d ³	42	29 to 91
M6 ±14d ³	141	92 to 232
M12 ±14d ³	323	233 to 414
M18 ±14d ³	506	415 to 597
M24 ±14d ³	689	598 to 871
M36 ±14d ³	1054	872 to 1236
M48 ±14d ³	1419	1237 to 1601
M60 ±14d ³	1784	≥ 1602

Infusion Day 1 = start date of tisagenlecleucel infusion

¹ for patients who did not receive LD chemotherapy, this window is ≤-2

² for patients who did not receive LD chemotherapy, this window is -1 to 1 pre-infusion

³ Sample collection based on randomization date, therefore planned timing in relation to infusion is calculated assuming that infusion happens 6 weeks after randomization

Table 5-6 shows the defined time windows for immunogenicity samples based on the TIS with timings based on the infusion date.

Table 5-6 Time windows for immunogenicity analyses based on tisagenlecleucel infused set

Time Window	Planned visit timing (infusion day)	Time Window Definition (Infusion day)
Humoral & Cellular Immunogenicity		
Infusion -1d	-1	< Day 1 pre-infusion
Infusion +13d ±3d	14	Day 1 post infusion to 21
Infusion +28d ±7d	29	22 to 54
M4 ±14d*	80	55 to 110
M6 ±14d*	141	111 to 232
M12 ±14d*	323	233 to 414
M18 ±14d*	506	415 to 597
M24 ±14d*	689	598 to 1236

M60 ±14d* 1784 ≥ 1237

Infusion Day 1 = start date of tisagenlecleucel infusion

* Sample collection based on randomization date, therefore planned timing in relation to infusion is calculated assuming that infusion happens 6 weeks after randomization

Table 5-7 shows the defined time windows for PK samples based on the CKAS with timings based on the infusion date.

Table 5-7 Time windows for PK analysis based on CKAS

Time Window	Planned visit timing (Infusion day)	Time Window Definition (Infusion day)
CTL019 pharmacokinetics by q-PCR in peripheral blood		
Infusion (pre-infusion)	1	< Day 1 pre-infusion
Infusion +1d	2	Day 1 post-infusion to 3
Infusion +3d ±1d	4	4 to 5
Infusion +6d ±1d	7	6 to 9
Infusion +10d ±3d	11	10 to 12
Infusion +13d ±3d	14	13 to 18
Infusion +21d ±3d	22	19 to 25
Infusion +28d ±7d	29	26 to 35
Week 12 ±7d*	42	36 to 61
M4 ±14d*	80	62 to 110
M6 ±14d*	141	111 to 186
M9 ±14d*	232	187 to 277
M12 ±14d*	323	278 to 414
M18 ±14d*	506	415 to 597
M24 ±14d*	689	598 to 871
M36 ±14d*	1054	872 to 1236
M48 ±14d*	1419	1237 1601
M60 ±14d*	1784	≥ 1602
CTL019 pharmacokinetics by flow cytometry in peripheral blood		
Infusion +10d ±3d	11	Day 1 post infusion to 20
Infusion +28d ±7d	29	21 to 35
Week 12 ±7d*	42	≥ 36
CTL019 pharmacokinetics by q-PCR in bone marrow aspirate		
Week 12 ±7d*	42	≥ Day 1 post infusion

Infusion Day 1 = start date of tisagenlecleucel infusion

* Sample collection based on randomization date, therefore planned timing in relation to infusion is calculated assuming that infusion happens 6 weeks after randomization

Table 5-8 shows the defined time windows for PRO assessments for analyses based on the FAS with timings based on randomization date.

Table 5-8 Time windows for PRO analyses based on the full analysis set

Time Window	Planned visit timing (study day)	Time Window Definition (Study day)
SF-36v2, FACT-LYM, EQ-5D-5L		
D1 Randomization	1	≤ Study Day 1

Week 6 ±14d	42	2 to 63
Week 12 ±7d	84	64 to 133
M6 ±14d	183	134 to 228
M9 ±14d	274	229 to 319
M12 ±14d	365	320 to 456
M18 ±14d	548	457 to 639
M24 ±14d	731	640 to 913
M36 ±14d	1096	914 to 1278
M48 ±14d	1461	1279 to 1643
M60 ±14d	1826	≥ 1644

Study Day 1 = randomization date

6 Reference

1. Clopper CJ and Pearson ES (1934). The use of confidence or fiducial limits illustrated in the case of the binomial. *Biometrical*, 26, 404-413.
2. Brookmeyer R and Crowley J (1982). A Confidence Interval for the Median Survival Time. *Biometrics*, 38, 29 - 41.
3. Collet D (1994). *Modelling survival data in medical research*. London, Chapman & Hall.
4. Lee D, Gardner R, Porter DL, et al (2014) Current concepts in the diagnosis and management cytokine release syndrome. *Blood*; 124 (2): 188-195.
5. Xu Z, Zhen B, Park Y, Zhu B (2017). Designing therapeutic cancer vaccine trials with delayed treatment effect. *Stat Med*, 36(4): 592-605.
6. Zhang X (2013). Comparison of restricted mean survival times between treatments based on a stratified Cox model. *Bio-Algorithms and Med-Systems*; 9(4): 183-189.
7. Zhao L, Claggett B, Tian L, et al (2015). On the restricted mean survival time curve in survival analysis. *Biometrics*. 72, 215-221.