Clinical Development

CTL019 (tisagenlecleucel-T)

CCTL019C2201 / NCT02445248

A Phase II, single arm, multicenter trial to determine the efficacy and safety of CTL019 in adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL)

Statistical Analysis Plan Amendment 3

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Document History

Version	Date	Changes
0.1	08/27/2015	First draft to CTT review
0.2	10/07/2015	Incorporating CTT comments, sent to LF head review
0.3	11/23/2015	Incorporating LFH review comments, sent to CSB review
1.0	01/19/2016	Final version
2.0	02/23/2017	Amendment 1 Updates related to protocol Amendment 4 • Updated study design to align with protocol. • Clarified that the primary endpoint and secondary endpoints will be assessed in main cohort (US manufacturing). Additional analyses will also be done separately for cohort A (Fraunhoffer) and for both cohorts combined. • Updated the response evaluation criteria from [redacted] • Updated the timing of interim and primary analysis, changing the minimal follow up at the time of analysis from 6 months to 3 months • Added Efficacy analysis set • Updated Per-Protocol set [redacted] Updates related to analyses included in Pediatric ALL BLA • Clarify the sensitivity analyses on enrolled patients • Added analysis for hematopoietic cytopenia [redacted] • Updated PK analysis plan Updates related to the interim analysis • Added scope of interim analysis (Section 6) • Clarified that interim efficacy analysis (except OS) will be conducted on EAS. Updates related to analyses in breakthrough application • Added analysis of ORR based on BOR ignoring CR/PR at day 28 • Added sensitivity analysis for ORR excluding patients with CR at baseline Details/Clarification for Programming • Update partial date imputation rule for concomitant medication • Algorithm for censoring after missing two scheduled assessment • Algorithm for defining IPI risk factor category • Information for defining cohort, molecular subtype, double/triple hit subgroup
3.0	01/06/2017	Amendment 2 • Updated definition of analysis sets for more clarity

Version	Date	Changes

		• Added analysis population by endpoints in Section 6 to clarify the scope and presentation for primary and final analysis.
		• Updated definition of refractoriness.
		• Added additional analysis for response rate
		  ○ Response rate at Month 3, 6 and 9
		  ○ Comparative analysis between local and central review
		• Updated PK and immunogenicity analysis
		  ○ Moved dose response analysis to SCP
		  ○ Moved exposure response analysis to SCP
		  ○ Miscellaneous updated analysis of PK and immunogenicity
		• Updated subgroup analysis

4.0	09/20/2017	Addendum 1 • One subgroup analysis was added for primary endpoint of ORR as per FDA request. ○ Time from most recent relapse to CTL019 infusion: <=Median vs. >Median • New presentation of CRS information (including maximum CRS grade, time to onset of CRS; duration of CRS; time to Grade 3/4 CRS, concurrent infections [redacted] selected complications, [redacted]
5.0	01/29/2019	Addendum 2 • Updated the language in AESI section to include all identified and potential risks. The list of AESIs and their search criteria are provided in the program-level electronic Case Retrieval Strategy (eCRS) form. • One subgroup analysis was added for safety ○ Baseline total tumor volume: <=Median, >Median • Updated the subgroup categories of number of prior lines of anti-neoplastic therapy from '<=2 lines, 3-4 lines, >=4 lines' to '<=2 lines, >2 lines' • Removed the Kaplan-Meier analysis of time to first CRS onset
6.0	01/24/2023	Amendment 3 • Clarify scope for final CSR • Update the analysis for cytopenia per product-level standard

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ABC	Activated B-cell
AE	Adverse Event
AESI	Adverse events of special interest
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Curve
[redacted]	[redacted]
BOR	Best overall response
CAR	Chimeric antigen receptor
CCG	CRF Completion Guidelines
CI	Confidence Interval
CIF	Cumulative incidence function
C_{max}	Maximum concentration
[redacted]	[redacted]
CMR	Complete Metabolic Response
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
CSR	Clinical Study Report
CT	Computed tomography
CTC	Common toxicity criteria
CTCAE	Common Terminology Criteria for Adverse Events
DLBCL	Diffuse large B-cell lymphoma
DMC	Data monitoring committee
[redacted]	[redacted]
DOR	Duration of Response
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture
EFS	Event free survival
FAS	Full analysis set
GC	Germinal center-like
HSCT	Hematopoetic stem cell transplantation
ICF	Informed consent form
[redacted]	[redacted]
[redacted]	[redacted]
IPI	International Prognostic Index
IRC	Independent Review Committee
IRT	Interactive Response Technology
i.v.	Intravenous(ly)
IWRS	Interactive Web Response System
kg	Kilogram
KM	Kaplan Meier
LLOQ	Lower Limit of Quantification

LOQ	Limit of Quantification
LPLV	Last Patient Last Visit
LTFU	Long Term Follow Up
MedDRA	Medical Dictionary for Regulatory Authorities
mL	Milliliter
MRI	Magnetic Resonance Imaging
MRT	Mean Residence Time
ORR	Overall Response Rate
OS	Overall Survival
PAS	Pharmacokinetic analysis set
PCR	Polymerase Chain Reaction
PD	Progressive disease
PD	Pharmacodynamics
PET	Positron emission tomography
PFS	Progression Free Survival
PK	Pharmacokinetics
PMR	Partial Metabolic Response
PPS	Per Protocol Set
PR	Partial Response
[redacted]	[redacted]
PT	Preferred Term
QOL	Quality of Life
Q-PCR	Quantitative Polymerase Chain Reaction
r/r	Relapsed or refractory
RAP	Report and Analysis Plan
RCL	Replication competent lentivirus
RNA	Ribonucleic acid
SAE	Serious Adverse Event
SCT	Stem cell transplantation
SD	Stable Disease
[redacted]	[redacted]
SOC	System Organ Class
SPD	Sum of the product of the diameters
[redacted]	[redacted]
Tlast	Time of the last measurable concentration
T_{max}	Time to peak concentration
TNC	Total nucleated cells
TNF	Tumor Necrosis Factor
ULOQ	Upper Limit of Quantification
UNK	Unknown
VSV-G	Vesicular Stomatitis Virus, Glycoprotein
WBC	White blood cells

1 Introduction

This document describes the detailed statistical methodology for the study CTL09C2201: A Phase II, single arm, multicenter trial to determine the efficacy and safety of CTL019 in adult patients with relapsed and refractory diffuse large B-cell lymphoma. The data will be analyzed by Novartis and/or a designated CRO. It is planned that the data from all centers that participate in this protocol will be used. Three analyses are planned:

- Interim analysis: when 50 patients treated with CTL019 from US manufacturing facility (main cohort) have been followed for at least 3 months or discontinued earlier. No CSR will be written.
- Primary analysis: when 80 patients treated with CTL019 from US manufacturing facility (main cohort) have been followed for at least 3 months or discontinued earlier. Interim CSR will be written to support filing.
- Final analysis: when all patients treated with CTL019 have completed study or discontinued earlier.

2 Study design, objectives and endpoints

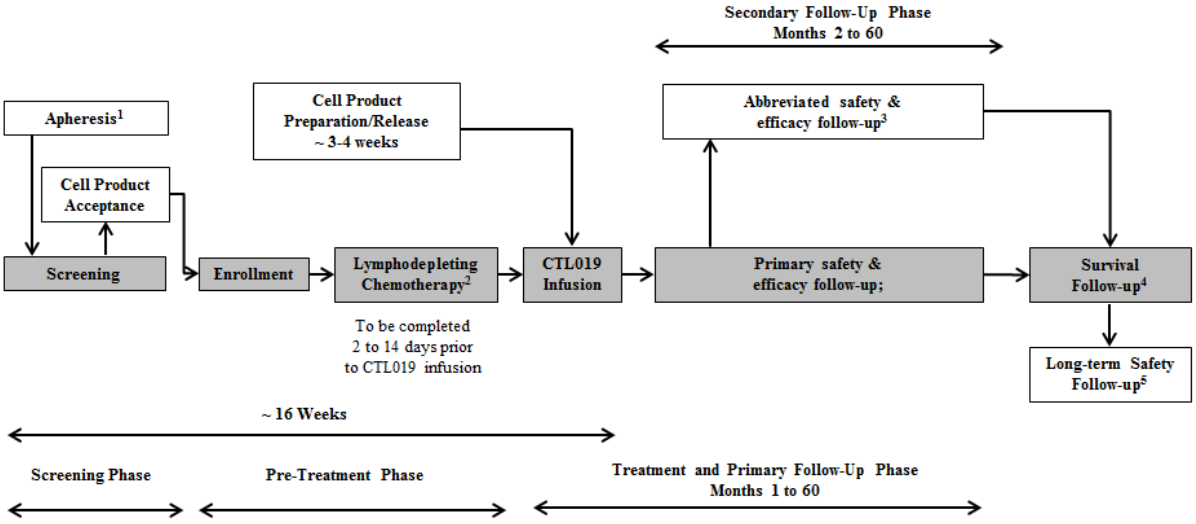
2.1 Study Design

The target population is comprised of adult patients with relapsed or refractory Diffuse Large B Cell Lymphoma. The study will have the following sequential phases for all patients (see Figure 2-1): Screening, Pre-Treatment (cell product preparation and lymphodepleting chemotherapy), Treatment and Primary Follow-up, Secondary Follow-up, and Survival Follow-up. Efficacy for all patients will be evaluated using CT/MRI based on the [redacted] Efficacy will be assessed at Day 28 and months 3, 6, 9, 12, 18, 24 months and then every 12 months for 5 years until documented disease relapse or disease progression. PET-CT will be performed at baseline and at Month 3. Due to the mechanism of action of CTL019, the Day 28 assessment should be interpreted in context of other clinical parameters that suggest true progression rather than pseudo-progression due to inflammatory changes and tumor swelling (De Velasco et al 2015). Although clinical guidelines (ESMO and NCCN) do not recommend routine imaging in patients in CR for longer than 2 years, in the context of this clinical trial an extended efficacy follow up by CT/MRI is justified. Safety will be assessed throughout the study.

One additional cohort has been added to the original main study cohort (80 patients treated with CTL019 manufactured at the Novartis manufacturing facility in Morris Plains, USA).

The additional cohort A will enroll approximately 18 patients to allow at least 15 patients infused with CTL019 manufactured at the Fraunhofer Institut für Zelltherapie.

Figure 2-1 Study design



1 Performed prior to Study Entry
2 As indicated per protocol
3 Only for patients who drop out of the Primary Follow-up before Month 60.
4 Patients will be followed for survival until the end of trial, or until they are enrolled in the long-term follow-up.
5 Long term safety follow-up conducted per health authority guidance under a separate protocol

Only following informed consent/assent and confirmation of all clinical eligibility criteria will the information of the patient's apheresis product ("pre-qualification") be transmitted to the manufacturing facility. The manufacturing facility will then evaluate the patient's apheresis product for acceptance. Enrollment is defined as the point at which a patient meets all clinical inclusion/exclusion criteria and the patient's apheresis product is accepted for manufacturing.

Prior to CTL019 cell infusion and after apheresis, one cycle of lymphodepleting therapy is planned, if patients are not already lymphopenic. The purpose of the chemotherapy is to induce lymphopenia in order to facilitate engraftment and homeostatic expansion of CTL019 cells. If patients have a White Blood Cell (WBC) count $\leq$ 1,000 cells/µL within one week prior to CTL019 infusion, lymphodepleting chemotherapy is not required.

CTL019 infusion will be given 2 to 14 days after completion of lymphodepleting chemotherapy, if lymphodepleting chemotherapy is required. CTL019 transduced T cells will be given as a single dose with a target of 5 x 10^8 (range 1-5 x 10^8) autologous CTL019 transduced cells via intravenous infusion. For patients with manufactured cell numbers falling below the above recommended dose ranges, CTL019 therapy will still be administered if product meets all other manufacturing release criteria.

Disease status, PK, [redacted] safety and survival will be assessed in the Treatment and Primary Follow-up phase for up to 5 years post CTL019 infusion. Patients who discontinue the Treatment and Primary Follow-Up Phase before month 60 will continue to be followed in the secondary follow-up phase in order to collect health authority requested data (e.g. protocol defined adverse events) up to 5 years after CTL019 infusion. For all patients who complete the primary follow-up or complete/prematurely discontinue from the primary or secondary follow-up phase, attempts to follow-up will be made to determine survival every 3 months post-

CTL019 infusion until end of study, or patient is enrolled in the long term follow-up study, whichever occurs first.

The end of study is defined as the last patient's last visit (LPLV), which is the last patient's Month 60 evaluation, or the time of premature withdrawal.

2.2 Study objectives and endpoints

Objectives and related endpoints are provided in Table 2-1 and detailed in the study protocol.

Table 2-1 Study objectives and endpoints

Objective	Endpoint
Primary:	
Evaluate the efficacy of CTL019 therapy in the main cohort	Overall response rate (ORR), which includes complete response (CR) and partial response (PR) as determined by IRC assessment in the full analysis set (FAS) of the main cohort In addition sensitivity analyses will be performed using the local investigator response assessments
Key secondary:	
Not applicable	Not applicable
Other secondary:	
Evaluate safety of CTL019	Type, frequency and severity of adverse events and laboratory abnormalities
Evaluate time to response	Time to response, i.e. time between date of CTL019 infusion until first documented response (CR or PR)
Evaluate duration of overall response (DOR)	Duration of response, i.e. the time from achievement of CR or PR, whichever occurs first, to relapse or death due to DLBCL
Evaluate event free survival (EFS)	EFS, i.e. the time from date of CTL019 infusion to the date of first documented disease progression or relapse, new treatment for lymphoma or death due to any cause
Evaluate progression free survival (PFS)	PFS, i.e. the time from date of CTL019 infusion to the date of first documented disease progression or death due to any cause
Evaluate overall survival (OS)	OS, i.e., the time from date of CTL019 infusion to the date of death due to any cause
Evaluate efficacy and safety in histological and molecular subgroups (GC, ABC, other)	ORR, PFS, OS, EFS, DOR and AEs in histological and molecular subtypes
Characterize the *in vivo* cellular PK profile (levels, expansion, persistence) of CTL019 transduced cells into target tissues (blood, bone marrow, cerebral spinal fluid and other tissues if available), summarized by clinical response	- PK parameters: Cmax, Tmax, AUCs, T1/2, Clast, Tlast and/or other relevant PK parameters in peripheral blood, bone marrow, as appropriate
Characterize immunogenicity (pre-existing (pre-dose) and post-infusion) in patient treated with CTL019	-Summary of immunogenicity(cellular and humoral)

Objective	**Endpoint**
Describe presence of RCL	- RCL by VSV-g q-PCR
Evaluate efficacy and safety in cohort A	ORR, PFS, OS, EFS, DOR and AEs in cohort A
Evaluate the Overall response rate for all patients treated	ORR in all patients treated

3 Definitions and general methodology

3.1 Definitions

3.1.1 Study drug and study treatment

Study drug is defined as CTL019 transduced cells.

Study treatment includes not only the study drug, i.e., CTL019 transduced cells, but also lymphodepleting chemotherapy.

3.1.2 Date of first administration of lymphodepleting chemotherapy

The date of first administration of lymphodepleting chemotherapy is defined as the first date when a non-zero dose of chemotherapy was administered and recorded on the "Concomitant Antineoplastic Therapy" eCRF for the indication "Lymphodepleting".

3.1.3 Date of infusion of study drug

The date of infusion of study drug is defined as the date when a non-zero dose of study drug (CTL019 transduced cells) was administered and recorded on the "Dosage administration record" eCRF.

3.1.4 Date of first study treatment

For patients who received lymphodepleting chemotherapy, the date of first study treatment is the date of first administration of lymphodepleting chemotherapy (as defined in Section 3.1.2); for patients who did not receive lymphodepleting chemotherapy, the date of first study treatment is the date of infusion of study drug (as defined in Section 3.1.3).

3.1.5 Study day

The study day will be calculated as the difference between the date of the assessment and the date of first infusion of CTL019 (**Day 1**) plus 1 for assessments on or after the date of first infusion. For assessment before the date of first infusion, the study day will be calculated as the difference between the date of the assessment and the date of first infusion of CTL019 (**Day 1**) *(Note: if an event happens before the first day of CTL019 infusion then the study day will be negative.)* For patients who did not receive CTL019 infusion, their study days will not be calculated.

The study day will be displayed in all relevant data listings.

3.1.6 Baseline

Baseline is the result of an investigation describing the "true" uninfluenced state of the patients.

For efficacy and safety evaluation, the last available assessment before CTL019 infusion is taken as "baseline" value or "baseline" assessment.

If patients have no value as defined above, the baseline results will be missing.

3.1.7 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 3-2. For each of the sources specific conditions listed in the second column of Table 3-1 have to be fulfilled to ensure that there was true contact with the patient.

No additional dates are allowed to be used, e.g. dates coming from concomitant medications, [redacted] etc.

Table 3-1 Last contact date data sources

Source data	Conditions
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 marked as 'done'.
Laboratory/PK collection dates	Sample collection marked as 'done'.
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: completely imputed dates will not be used to derive the last contact date. Partial date's imputation is allowed to be used for event (death) and for censoring date only if coming from Survival Follow-up eCRF page (see Section 5.5.6 for details).

3.1.8 Lost to follow-up

Patients will be considered as lost to follow-up for time to event analysis 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).

3.2 Data Included in the analysis

Data from all participating centers will be combined for the analyses.

The primary analysis will be performed after approximately 80 patients from main cohort have received CTL019 infusion and completed 3 months from study day 1 infusion or discontinued earlier. One interim analysis for futility and overwhelming efficacy will be performed after approximately 50 patients from main cohort have received CTL019 infusion and the last patient has completed 3 months from study day 1 infusion or discontinued earlier. Each analysis will use all data in the database up to the analysis cutoff date, determined prior to database lock.

Selected efficacy and safety analysis will be updated annually. A final Clinical Study Report (CSR) will be produced once all patients complete or discontinue from the study. Analyses

supporting primary and secondary objectives will be updated in the final CSR. Details for statistical outputs selection will be reflected in the Tables, Figures and Listings Shells of the final CSR.

3.3 Definitions of analysis sets

The analysis sets to be used are defined as below. Unless otherwise specified, the Efficacy analysis set (EAS) will be used for ORR, DOR and TOR. The Full analysis set (FAS) will be used for PFS, EFS and OS. The Safety Set will be used for all safety analyses, unless otherwise specified. The Pharmacokinetic analysis set (PAS) will be used for pharmacokinetics analyses.

Analysis population for different endpoints and different planned analysis are specified in Section 6.

Screened Set

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

Enrolled Set

The Enrolled Set comprises all patients who are enrolled in the study. Enrollment is defined as the point at which the patient meets all inclusion/exclusion criteria, and the patients' apheresis product is accepted for manufacturing. In case of protocol deviation such that patients are enrolled without meeting all inclusion/exclusion criteria, such patients will still be considered in the Enrolled Set, if the patients' leukapheresis product is received and accepted by the manufacturing facility.

Full Analysis Set (FAS)

The Full Analysis Set (FAS) comprises all patients who received infusion of CTL019.

Efficacy Analysis Set (EAS)

The Efficacy Analysis Set comprises a subset of patients in FAS who received CTL019 infusion at least 3 months (90 days) prior to data-cut date.

Safety Set

The Safety Set comprises all patients who received infusion of CTL019. Note that the Safety Set and FAS are the same for this study.

Per-Protocol Set (PPS)

The Per-Protocol Set (PPS) consists of a subset of the patients in the EAS (at time of interim and primary analysis) or FAS (at time of final analysis) who are compliant with major requirements of the study protocol.

Major protocol deviations leading to exclusion from the PPS include:

- Diagnosis of disease other than DLBCL at baseline;
- Missing or incomplete documentation of disease at baseline;

In addition, patients who receive a dose less than the minimum target dose 1×10^8 CTL019 transduced cells will also be excluded.

Pharmacokinetic Analysis Set (PAS)

The CTL019 Pharmacokinetic Analysis set (PAS) consists of patients in FAS who have at least one sample providing evaluable cellular kinetic data. The PAS will be used for summaries (tables and figures) of cellular kinetic data.

[redacted]

3.4 Response evaluation for DLBCL

The DLBCL response guideline is outlined in the Protocol Appendix 1 - Guidelines for efficacy evaluation in diffuse large B cell lymphoma and follicular lymphoma studies (Based on [redacted]), hereafter referred to as [redacted].

3.4.1 Overall radiological response at each assessment

Overall radiological response at each assessment is calculated as shown in Table 3-2. Please refer to the [redacted] for details.

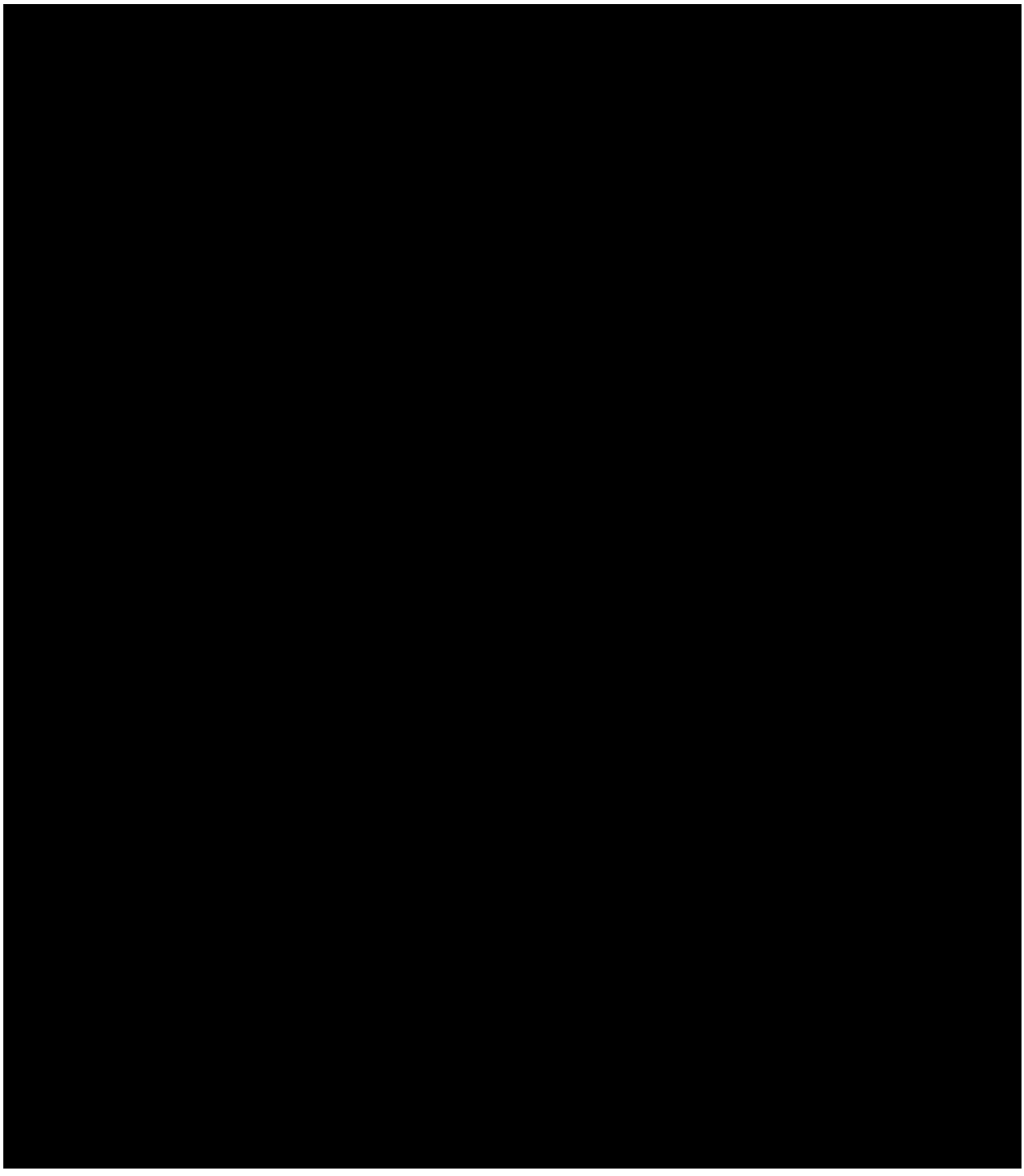
Table 3-2 Overall radiological response based on CT at each assessment

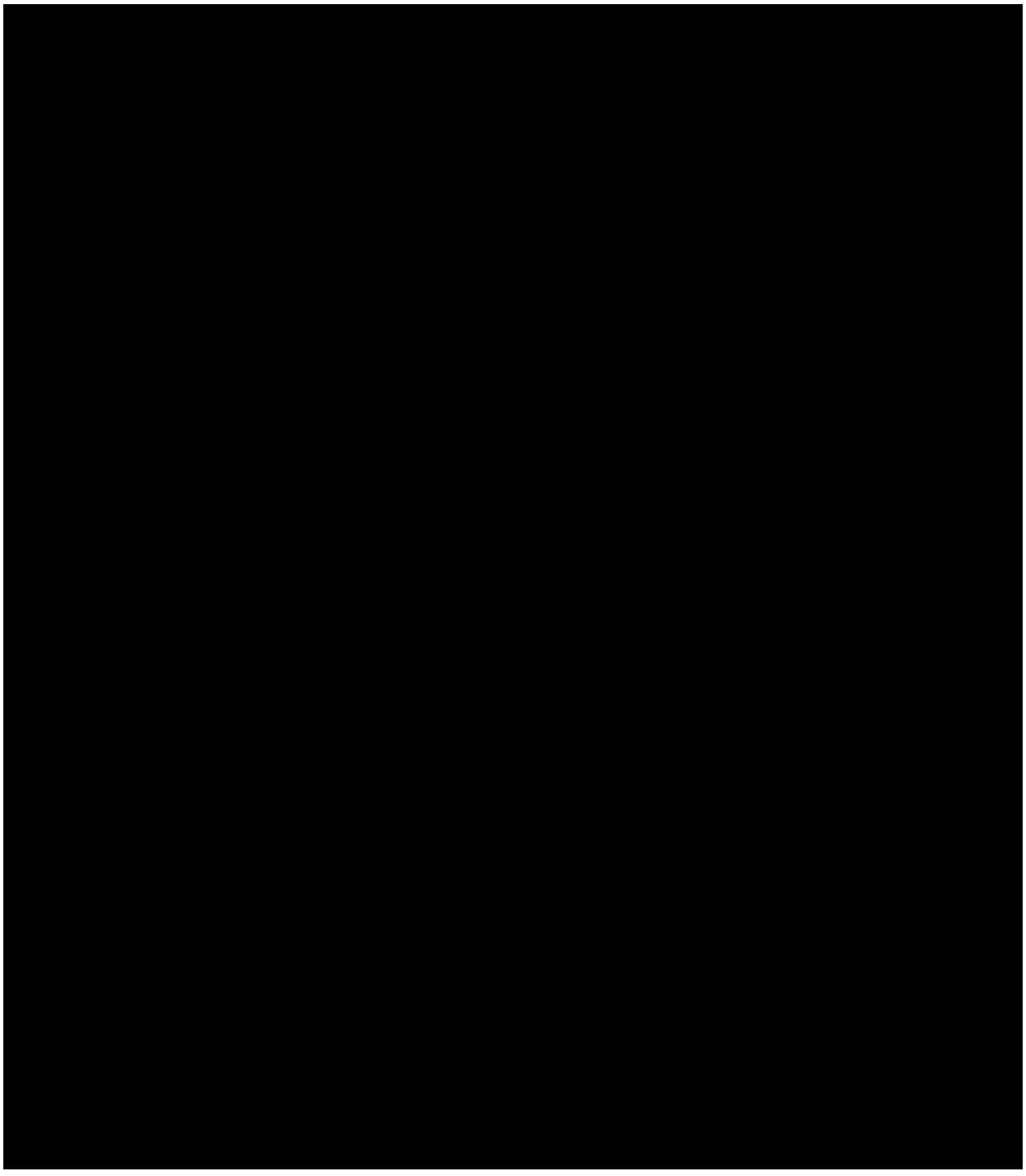
Index lesions	Non-index lesions[1]	New lesions	Overall radiological response
CR	CR	No	CR
CR	SD	No	PR
PR	CR or SD	No	PR
SD	CR or SD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

[1] If no non-index lesions are present at baseline, then this column is not used in evaluating overall radiological response.

3.4.2 Overall disease response at each assessment

[redacted]





3.4.3 Best Overall disease response

The best overall disease response (BOR) is the best disease response recorded from date of infusion until progressive disease or start of new anticancer therapy (including ASCT), whichever comes first, and will integrate metabolic and radiologic responses.

A patient will have a best overall disease response of **CR** if they had CR as overall disease response for at least one of the assessments.

A patient will have a best overall disease response of **PR** if at least one overall response of PR is available (and the patient would not qualify for CR).

A best overall disease response of **SD** will be declared when at least one SD assessment is available at least 4 weeks after CTL019 infusion (and the patient would not qualify for CR or PR).

A patient will have a best overall disease response of **PD** if the progressive disease was observed less than 14 weeks after CTL019 infusion (and the patient does not qualify for CR, PR or SD).

If a patient does not qualify for CR, PR, SD or PD, then their best disease response will be **Unknown** (UNK).

3.4.4 Disease response and response rate (ORR) at month X (X=3, 6 and 9)

Disease response at month X is defined as the overall disease response evaluated at month X within protocol specified window. Response will be imputed follow the order of the rules below:

1. If patient start new cancer therapy prior to month X, then the response will be imputed as UNK
2. If an PD was observed earlier, then the response will be imputed as PD
3. If month X evaluation is not available, then the response will be imputed as
    - CR, if both previous and next evaluations are available and show CR.
    - PR, if previous evaluation shows PR and next evaluation shows PR or better.
    - UNK, Otherwise.

The denominator for calculating ORR and CR rate at month X will be based on the number of patients who had infused at least X months prior to the data cut-off.

3.5 Time-to-event definitions

General rule for the calculation of the time to event interval is:

Time to event = event date - start date + 1 (in days)

When no post-baseline assessments of the event are available, the date of CTL019 infusion will be used as end date when time is to be censored at last post-baseline response assessment, i.e. time to event variables will never be negative.

Often censoring time is determined based on date of adequate response assessment. Any response assessment is considered to be adequate if the assessment was performed and the outcome of the assessment was other than “unknown” or “not done”.

4 Statistical methods used in reporting

4.1 General presentation of descriptive summaries

Categorical data (e.g., gender, race, etc.) will be summarized by means of contingency tables; a missing category will be included as applicable. Percentages will be calculated using the number of patients in the relevant population or subgroup as the denominator.

Continuous data (e.g., age, body weight, etc.) will be summarized by appropriate descriptive statistics (i.e. mean, standard deviation, median, minimum, and maximum).

4.2 Cohort

Patient cohort will be identified by culture ID collected on 'Cryopreservation of Cell Doses - Primary Product' CRF. Patients with culture ID started with 'MP' are from main cohort (manufactured by Morris Plain, USA) and patients with culture ID started with 'FH' are from cohort A (manufactured by Fraunhofer, Germany).

4.3 Patient disposition

Patient disposition will be summarized for the following phases: 1) screening phase for the Screened Set; 2) pre-treatment phase for the Enrolled Set, 3) treatment and primary follow-up phase for the FAS and 4) secondary follow-up phase for the FAS. The patient disposition for each phase as specified will be summarized for all patients who entered that phase. The number and percentage of patients in each of the categories as listed for "End of Phase Disposition eCRF" pages will be tabulated and listed. Patients who have entered any study phase but have not completed/discontinued will be listed as appropriate.

For the screening phase, the clinical eligibility criteria that were not met by patients will also be tabulated. In addition, the number and percentage of patients who enrolled in the long term follow-up study will be summarized.

In addition, a high level disposition summary including all phases will be provided for all screened patients.

Duration of primary follow-up and total duration of study follow-up will be summarized descriptively. The number of patients in the following categories of duration of follow-up will also be tabulated : <3 months, 3 months to <6 months, 6 months to <12 months, 12 months to <24 months, >=24 months.

4.4 Background and demographic characteristics

The Enrolled set will be used for all baseline disease characteristics and demographic summaries. Patients infused and patients not infused will be presented side by side.

4.4.1 Basic demographics data

Demographic and other baseline data will be listed by patient and/or summarized descriptively.

4.4.2 Medical history

Medical history and ongoing conditions, including cancer-related conditions and symptoms at the time of informed consent will be summarized and listed. Separate summaries will be presented for ongoing and historical medical conditions. The summaries will be presented by primary system organ class and preferred term. Medical histories are coded using the medical dictionary for regulatory activities (MedDRA) terminology.

4.4.3 Prior anti-neoplastic therapy

Number and percentage of patients with prior anti-neoplastic medications/therapies/surgeries will be summarized. Prior anti-neoplastic medications will be summarized by ATC class, and preferred term. All prior anti-neoplastic medications, radiotherapies, surgeries and SCT will be listed.

Patients will be classified by their prior treatment response:

- Refractory to last line
  - Refractory to all lines: Patients who have never achieved CR or PR prior to study.
  - Not refractory to all lines: Patients who did not achieved CR or PR at the last line of therapy prior to study but have achieved CR or PR before.
- Relapsed to last line: Patients had a CR or PR from last line of prior therapy and relapsed prior to the study

4.4.4 International Prognostic Index (IPI) factor

IPI were determined by the answers (Yes, No and Unknown) of first five questions on 'Prognostic Factors' CRF

- Age greater than 60 years old
- ECOG performance status >=2
- More than a site of extranodal disease
- Elevated LDH > upper limit of normal
- Disease stage III/IV

IPI factors are summarized by category, based on number (Y) of questions with "Yes" and number (N) of questions with "No"

- >=2; if Y>=2
- < 2; if N>=4
- Unknown; otherwise

4.4.5 Others

All other data collected at baseline will be listed.

4.5 Protocol deviation summaries

The number and percentage of patients in the Full Analysis Set with any protocol deviation will be tabulated by the deviation category. Major protocol deviations leading to exclusion from the PPS will be summarized.

All protocol deviations will be listed.

4.6 Treatments (study treatment, rescue medication, other concomitant therapies, compliance)

The total cells infused (both cells) and total transduced CTL019 cells infused (both cells and cells/kg) will be listed and summarized using descriptive statistics.

Patients will be categorized as below, within or above the prescribed dose range. Patients with dose interruptions, as recorded in the dosage administration record eCRF, will be summarized. Because the study drug of CTL019 is administered via one time infusion, no specific compliance will be summarized other than the CTL019 dose administration.

Prior and concomitant medications and significant non-drug therapies prior to and after the start of infusion will be listed by patient and summarized by ATC class and preferred term.

Antineoplastic therapies, including the lymphodepleting chemotherapies, received after enrollment but prior to infusion will be listed. Patients will also be summarized by the types of lymphodepleting chemotherapies received.

Transfusions during the study will be listed.

Rescue medications are medications given for severe CRS due to CTL019 cells. [redacted]

4.7 Efficacy evaluation

4.7.1 Primary efficacy endpoint

The primary objective of the study is to evaluate the efficacy of CTL019 therapy as measured by overall response rate (ORR), which includes complete response (CR) and partial response (PR) as determined by IRC assessment in the FAS in main cohort (patients treated with CTL019 from US manufacturing facility).

The study will be ongoing at the time of interim analysis and primary analysis, when 50 and 80 patients respectively from main cohort had 3 month follow-up or discontinued earlier. Therefore EAS will be used to assess the primary endpoint to these milestones to ensure that patients included in the analysis had the opportunity to be followed-up for 3 months.

FAS will be used for the final update of the primary endpoint after all infused patients in the main cohort have been followed 3 months or discontinued earlier.

In addition, sensitivity analysis will be performed using the local investigator response assessments instead of the IRC assessment.

4.7.1.1 Variable

The primary endpoint is the ORR as determined by IRC assessment. The ORR is defined as the proportion of patients with a best overall disease response of CR or PR, where the best overall disease response is defined as the best disease response recorded from CTL019 infusion until progressive disease or start of new anticancer therapy (including ASCT), whichever comes first.

Best overall response will be assigned according to the following order:

1. CR
2. PR
3. SD
4. PD
5. Unknown

The best overall disease response for a patient is always calculated, based on the sequence of overall disease responses.

See also the Section 3.4.3 for details regarding the definition of overall disease response.

4.7.1.2 Statistical hypothesis, model, and method of analysis

The primary efficacy analysis will be performed by testing the null hypothesis of ORR being less than or equal to 20% against the alternative hypothesis that ORR is greater than 20% at overall one-sided 2.5% level of significance, i.e.,

$$H_0: p \leq 0.2 \text{ vs. } H_a: p>0.2$$

The ORR will be summarized along with the 2-sided 95% exact Clopper-Pearson confidence intervals. Taking into account the interim analysis (see Section 4.16), the study will be considered successful if the lower bound of the 2-sided 95.28% exact confidence interval for ORR is greater than 20%, so that the null hypothesis that the ORR is less or equal to 20% can be rejected.

4.7.1.3 Handling of missing values/censoring/discontinuations

Patients in this study who are of unknown clinical response will be treated as non-responders. See also the Novartis guideline for efficacy evaluation in lymphoma studies (based on [redacted]) (Protocol Appendix 1) for more details.

Other missing data are simply noted as missing on appropriate tables/listings.

The censoring rules for time to event endpoints are specified in the corresponding sections in Section 4.6.2.

[redacted]

[redacted]

4.7.1.5 Subgroup analysis

Subgroup analyses will be performed on the following based on the patient's baseline status:

- Age: < 40 years, ≥40 years to <65 years, ≥ 65 years
- Gender: Male, Female
- Race: White, Asian, Black, Other
- Ethnicity: Hispanic or Latino, Other
- Prior response status: Refractory to last line, relapsed to last line
- IPI at enrollment: <2 risk factors, ≥2 risk factors
- Number of prior lines of anti-neoplastic therapy: <=2 lines, >2 lines
- Stage of disease at baseline: I/II, III/IV
- Prior HSCT therapy: yes or no
- Molecular subtype: GC, ABC and other.
- Rearrangements in MYC/BCL2/BCL6 genes: Double/Triple hits, Other
- Time from most recent relapse to CTL019 infusion: <=Median vs. >Median

Subgroup analyses will only be performed if at least 5 patients are present in each subgroup. Some grouping of classes will be considered if there are too few patients in some subgroups.

[redacted]

4.7.2 Secondary efficacy

4.7.2.1 Key secondary objective

Not applicable. No formal hypothesis testing is planned other than for the primary objective.

4.7.2.2 Other secondary efficacy objectives

IRC assessment will be used in the main analysis of secondary endpoints that involve disease response. GAP analysis will be provided for time to event endpoints.

4.7.2.2.1 Duration of overall response (DOR)

Duration of response (DOR) applies only to patients whose best overall disease response was CR or PR. It is defined as the time from the date of first documented disease response (CR or PR) to the date of first documented progression or death due to DLBCL. If a patient has not had an event, duration of overall response is censored at the date of the last adequate assessment.

In case a patient does not have progression or death due to DLBCL 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 censoring reason could be:

- Ongoing without event
- Lost to follow-up
- Withdrew consent
- New anticancer therapy (also see below for handling HSCT)
- Event documented after at least two missing tumor assessments
- Adequate assessments no longer available

In the main analysis of DOR, death due to reason other than DLBCL will be considered as a competing risk event to other events of interest (progression or death due to DLBCL). In this analysis, the median response duration as well as proportion of patients without events following response (progression or death due to DLBCL) at 3, 6, 9, 12 months, etc. will be presented with 95% confidence intervals using the cumulative incidence function (CIF). Distribution of DOR will also be estimated using the Kaplan-Meier method in which death due to reason other than DLBCL will be censored.

As HSCT is an important treatment option in responding patients, it is appropriate to consider the date of HSCT as censoring date, instead of censoring at the last tumor assessment date. If a patient received HSCT after a CR or PR, relapse or survival status after HSCT will be recorded on the corresponding follow-up eCRFs, although data on individual disease response components (e.g. CT scan) will not be collected. In such cases, the date of relapse or death (if due to DLBCL) after HSCT will be used for the calculation of DOR as a sensitivity analysis.

Distribution of DOR will be estimated using the Kaplan-Meier method and the median response duration as well as proportion of patients without event at 3, 6, 9, and 12 months will be presented along with 95% confidence interval.

In addition, DOR may be summarized separately for patients with best response CR and those with best response PR, if there are sufficient patients in each of these two groups.

4.7.2.2.2 Event free survival (EFS)

Event free survival (EFS) is the time from date of first CTL019 infusion to the earliest of the following (note the definition of events is not exactly the same as the Novartis modified Cheson criteria):

- Death from any cause
- Disease progression or relapse (as defined in section 3.4.2)
- New anticancer therapy for lymphoma, excluding HSCT

In case a patient does not have any of the above events prior to data cutoff, EFS is censored at the last adequate response assessment date on or prior to the earliest censoring event. The censoring reason could be

- Ongoing without event
- Lost to follow-up
- Withdrew consent
- HSCT (see below for handling of HSCT)
- Event after at least two missing scheduled disease assessment
- Adequate assessments no longer available

Patients who proceed to HSCT after CTL019 infusion will be censored at the time of HSCT in the main analysis of EFS. In addition, a sensitivity analysis of EFS will be performed without censoring for HSCT.

The distribution function of EFS will be estimated using the KM method. The median EFS along with 95% confidence intervals will be presented if appropriate.

4.7.2.2.3 Progression free survival (PFS)

Progression-free survival (PFS) is defined as the time from the date of first CTL019 infusion to the date of event defined as the first documented progression or death due to any cause. If a patient has not had an event, progression-free survival is censored at the date of the last adequate assessment.

In case a patient does not have progression or death prior to data cutoff, PFS will be censored at the date of the last adequate assessment on or prior to the earliest censoring event. The censoring reason could be:

- Ongoing without event
- Lost to follow-up
- Withdrew consent
- New anticancer therapy (see below for handling of HSCT)
- Event documented after at least two missing tumor assessments
- Adequate assessments no longer available

In the main analysis of PFS, patients who proceed to HSCT after CTL019 infusion will be censored at the time of HSCT. In addition, a sensitivity analysis of PFS will be performed without censoring for HSCT.

PFS will be estimated using the Kaplan-Meier method and the median PFS as well as proportion of patients without event at 3, 6, 9, and 12 months will be presented along with 95% confidence interval.

4.7.2.2.4 Time to response

Time to overall disease response (CR or PR) is defined as the time from the date of CTL019 infusion to the date of first documented disease response (CR or PR). The analysis will include all responders.

Time to response will be estimated using the Kaplan-Meier method and the median time to response will be presented along with a 95% confidence interval.

The following time to response may be explored if there are sufficient patients in the corresponding patient group: time from PR to CR (for patients with PR followed by CR); time from date of CTL019 infusion to PR (for all patients who had PR, regardless of whether it's followed by CR); Time from date of CTL019 infusion to CR (for patients who had CR)

4.7.2.2.5 Overall survival (OS)

Overall survival (OS) is the time from date of first CTL019 infusion to date of death due to any reason. If a death has not been observed by the date of analysis cutoff, OS will be censored at the date of last contact.

OS will be assessed in all patients (FAS). The distribution function of OS will be estimated using the Kaplan Meier (KM) method. The median OS and the proportion of patients alive at 3, 6, 12, 18, 24, 36, 48 and 60 months with 95% confidence intervals will be presented.

4.7.2.2.6 Efficacy in histological and molecular subgroups

The clinical efficacy outcomes (ORR, PFS, OS, EFS and DOR) will be summarized descriptively for each of the histological and molecular subgroups, if there are at least 5 patients in each of the group:

- Histological subgroups: Diffuse Large B-cell lymphoma, not otherwise specified (NOS), Transformed lymphoma and other.
- Molecular subgroups: germinal center (GC), activated B-cell (ABC) and other.

[redacted]

[redacted]

4.8 Safety evaluation

4.8.1 Analysis set and reporting periods for the analyses

Table 4-2 summarizes the mutually exclusive safety reporting periods as well as the patients to be included in each of the segments. Note that the post-infusion period will be the main period of safety reporting (see Section 4.7.2 for details).

Table 4-1 Safety reporting periods

Period	Definition	Patients to be included
Pre-treatment period	From day of patient's informed consent to the day before first lymphodepleting chemotherapy dose or the pre-infusion visit if the lymphodepleting chemotherapy is not given	Screened patients
Lymphodepleting period (note: this period only applies to patients who received lymphodepleting chemotherapy)	From the first day of lymphodepleting chemotherapy • to the day before infusion of CTL019, for patients who received infusion, or • to the earlier of date of discontinuation and 30 days after last dose of lymphodepleting chemotherapy for patients who didn't receive infusion of CTL019	All patients who received lymphodepleting chemotherapy
Post-infusion period	Starting at day of first CTL019 infusion until end of study	Safety Set

4.8.2 Adverse events (AEs)

Reporting of AEs (except for CRS) will be based on MedDRA (latest version per database lock) and Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. The grading of CRS will be based on protocol specific grading scales (Protocol section 6.2.4.2, Table 6-1).

Summary tables for AEs will be provided for AEs that started or worsened during the post-infusion period, i.e. the ***CTL019-treatment-emergent*** AEs. However, all safety data (including all observation periods as defined in Section 4.7.1) will be listed and with the period (as defined in Section 4.7.1) flagged for the starting date of the AE.

The incidence of CTL019-treatment-emergent AEs (new or worsening during the post-infusion period) will be summarized by system organ class, preferred term, severity (based on CTCAE grades), and relation to study drug. A patient with multiple CTC grades for an AE will be summarized under the maximum CTC grade recorded for the event. The frequency of CTC grade 3 and 4 AEs will be summarized separately.

Deaths and serious adverse events will be listed by patient and tabulated by primary system organ class and preferred term.

Adverse events of special interest (AESI) include all important identified and potential risks of tisagenlecleucel. The list of AESIs and their search criteria will be 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.

Post-infusion period:

The following AE summaries will be produced for the Safety Set and displayed by timing of onset: Within 8 weeks post first tisagenlecleucel infusion, 8 weeks to 1 year post first tisagenlecleucel infusion, >1 year post first tisagenlecleucel infusion, and any time post first tisagenlecleucel infusion.

- Adverse events, regardless of study drug relationship, by primary system organ class, preferred term and maximum grade
- Adverse events, suspected to be study drug related, by primary system organ class, preferred term and maximum grade
- Deaths post infusion during study follow-up, by primary system organ class and preferred term
- Serious adverse events, regardless of study drug relationship, by primary system organ class and preferred term and maximum grade
- Serious adverse events, suspected to be study drug related, by primary system organ class and preferred term and maximum grade
- Adverse events of special interest (AESI) based on identified risks, regardless of study drug relationship, by group term, preferred term and maximum grade
- Adverse events of special interest (AESI) based on identified risks, suspected to be study drug related, by group term, preferred term and maximum grade
- Adverse events of special interest (AESI) based on potential risks, regardless of study drug relationship, by group term, preferred term and maximum grade
- Adverse events of special interest (AESI) based on potential risks, suspected to be study drug related, by group term, preferred term and maximum grade
- Adverse events leading to study discontinuation, regardless of study drug relationship, by primary system organ class and preferred term
- Non-Serious Adverse events, regardless of study drug relationship, by primary system organ class and preferred term

Lymphodepleting period:

In addition, AEs that started or worsened during the lymphodepleting period will be summarized for all patients in the Enrolled Set who received lymphodepleting chemotherapy. The following tables will be produced:

- Adverse events, regardless of study treatment relationship by primary system organ class and preferred term
- Serious adverse events, regardless of study treatment relationship by primary system organ class and preferred term
- Adverse events, with suspected study treatment relationship by primary system organ class and preferred term

- Serious adverse events, with suspected study treatment relationship by primary system organ class and preferred term

Pre-treatment period:

AEs that started or worsened during the pre-treatment period will be separately summarized for the Enrolled Set:

- Adverse events, by primary system organ class, preferred term and maximum grade
- Serious adverse events, by primary system organ class and preferred term

Detailed information regarding the CRS will be summarized: maximum CRS grade, time to Grade 3/4 CRS, concurrent infections, [redacted] hypotension, use of fluid resuscitation, use of pressor support, [redacted] etc. If there is sufficient number of CRS events, separate summaries may be provided by best overall response.

4.8.3 Laboratory abnormalities

For laboratory tests covered by the CTCAE, the study's biostatistics and reporting team will grade laboratory data accordingly. For laboratory tests covered by CTCAE, a 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, results will be graded by the low/normal/high classifications based on laboratory normal ranges.

The following summaries will be generated separately for hematology and laboratory tests for Safety Set:

- Shift tables using CTCAE grades to compare baseline to the worst post-infusion value
    - for laboratory tests where CTCAE grades are not defined, shift tables using the low/normal/high/(low and high)
- Change from baseline to the worst post-infusion value, with descriptive statistics of baseline value, worst post-infusion value and the change.

The following listings will be provided for Enrolled Set.

- Listing of patients with laboratory abnormalities of CTC grade 3 or 4 with the corresponding CTC grades and the classifications relative to the laboratory reference ranges.
- Listing of all laboratory data with values flagged to show the corresponding CTC grades and the classifications relative to the laboratory reference ranges.

The shift tables will be generated by timing: Within 8 weeks post CTL019 infusion, >8 weeks to 1 year post CTL019 infusion, >1 year post CTL019 infusion, and any time post first tisagenlecleucel infusion.

In addition, percentage of patient with Grade 3 or 4 hematopoietic cytopenias 28 days post CTL019 infusion will be summarized. Among patients with Grade 3 or 4 hematopoietic cytopenias 28 days post CTL019 infusion, the timing of resolution to Grade 2 or below will be summarized via Kaplan-Maier method. Grading of cytopenias will be derived using lab results

in absolute lymphocytes (hypo), absolute neutrophils (hypo), hemoglobin (hypo), platelet count (hypo) or WBC (hypo) according to CTCAE 4.03. If a patient did not achieve resolution at the last lab assessment, timing of resolution will be censored at the last assessment. The median time to resolution and KM estimates of % unresolved cases at different time point (month 2, month 3 and etc.) will be summarized. The same analysis (summary and timing of resolution analysis) will also be generated for hematopoietic cytopenias 4 weeks post CTL019 infusion. The "4 weeks" is defined as the Week 4 visit day (i.e., Day 28) plus time window allowed per study protocol (i.e., 7 days).

The following listings will be provided for Enrolled Set.

- Listing of patients with laboratory abnormalities of CTC grade 3 or 4 with the corresponding CTC grades and the classifications relative to the laboratory reference ranges.
- Listing of all laboratory data with values flagged to show the corresponding CTC grades and the classifications relative to the laboratory reference ranges.

4.8.4 Cytokine release syndrome and anti-cytokine therapies

To explore the relationship between CRS and other endpoints, the goal of this statistical analysis should be considered as the generation of new scientific hypotheses and observing new trends, since the studies are not adequately powered to propose a scoring system.

Clinical [redacted] data will be analyzed to potentially identify an early predictive score which reflects the risk of developing severe cytokine release syndrome. Only parameters that can be potentially utilized in clinical setting by treating physicians will be considered for the score development.

Detailed information regarding the CRS will be summarized by disease response from IRC assessment. Information summarized includes: maximum CRS grade, time to onset of CRS; duration of CRS; time to Grade 3/4 CRS, concurrent infections, [redacted], selected complications, [redacted], etc.

In addition, time to resolution of the first CRS will also be summarized using KM method for patients with CRS. In case the end date of a CRS is missing, it will be censored / imputed as the minimum of the following dates: the cut-off date, end of study evaluation (i.e., completion of the last phase of the study), date of death (if applicable).

Peak cytokine level, time to high fever onset, CTL019 PK parameters (e.g. Cmax and AUC0-d28), [redacted] and CTL019 dose administered will be plotted against the maximum CRS grade using strip plot as appropriate. [redacted]

4.8.5 Other safety data

Vital signs will be collected as clinically needed. Presence of detectable RCL will be tested by VSV-G at protocol scheduled assessments. All safety data will be listed.

4.8.6 Safety subgroup analysis

Key safety summaries for adverse events regardless of relationship to study drug by System Organ Class (SOC) and Preferred Term (PT), and AESI will be repeated on the Safety Set in the following subgroups:

- Age: < 40 years, ≥ 40 years to <65 years, ≥ 65 years
- Gender: Male, Female
- Race: White, Asian, Black, Other
- Ethnicity: Hispanic or Latino, Other
- Prior HSCT therapy: yes or no
- Molecular subtype: GC, ABC and other.
- Stage of disease at baseline: I/II, III/IV
- Baseline total tumor volume: <=Median, >Median

The objective of carrying out these subgroup analyses is to identify safety problems that are limited to a subgroup of patients or 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.

4.9 Pharmacokinetic analysis

PAS will be used for all [redacted] PK summaries (Table and figures).

The following parameters or concentration time profiles will be displayed graphically:

CTL019 concentration versus time in peripheral blood, bone marrow and CSF (if available) as determined by qPCR [redacted]

The cellular kinetic parameters (Table 4-2) were estimated from the individual concentration versus time profiles using a non-compartmental approach within Phoenix® (Pharsight, Mountain View, CA). Non-quantifiable concentrations imputed to zero were included exclusively for the estimation of partial AUCs (eg. AUC0-28d) using the conventional linear trapezoidal approach. The apparent half-life was derived from concentration time profiles on a semi-logarithmic scale and hence the imputed values cannot be included in the estimation. [redacted] When a geometric mean was presented, it was stated as such. A range of values was presented for selected variables. For Tmax, only median values and ranges were given.

Table 4-2 Noncompartmental pharmacokinetic parameters

AUC 0 - Tmax	The AUC from time zero to T_{max} in peripheral blood (% or copies/ µg x days)
AUC Tmax - 28d or M3	The AUC from time Tmax to day 28 or M3 or other disease assessment days, in peripheral blood (% or copies/ µg x days)
AUC 0 - 28d or M3	The AUC from time zero to day 28 or M3 or other disease assessment days, in peripheral blood (% or copies/ µg x days)
AUC0-180d	The AUC from time zero to 180 days in peripheral blood (% or copies/ µg x days)
Cmax	The maximum (peak) observed in peripheral blood or other body fluid drug concentration after single dose administration (% or 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 disposition phase slopes (alpha, beta, gamma etc.) of a semi logarithmic concentration-time curve (days) in peripheral blood
Clast	The last observed quantifiable concentration in peripheral blood (% or copies/ µg)
Tlast	The time of last observed quantifiable concentration in peripheral blood (days)

[redacted]

[redacted]

4.9.5 Immunogenicity

Humoral immunogenicity assessment will include prevalence of immunogenicity (patients with pre-existing antibodies that bind to CTL019) and incidence of immunogenicity (patients with treatment-induced or treatment-boosted antibodies that bind to CTL019), together with antibody titers. Data will be further fractionated to determine proportion of patients who make transient versus sustained antibody responses. The assay for humoral immunogenicity will be a cell-based assay, detecting antibodies that bind to a Jurkat cell line transfected with the CTL019 construct. This cell line stably expresses the complete CTL019 sequence and can be used to detect antibodies that bind to any epitope on the extracellular domain of the protein.

Humoral immunogenicity:

The proportion of humoral immunogenicity positive and negative patients will be summarized by time points. Summary statistics will be presented for CTL019 cellular kinetic parameters for qPCR by anti-CTL019 antibody post-infusion status (positive or negative).

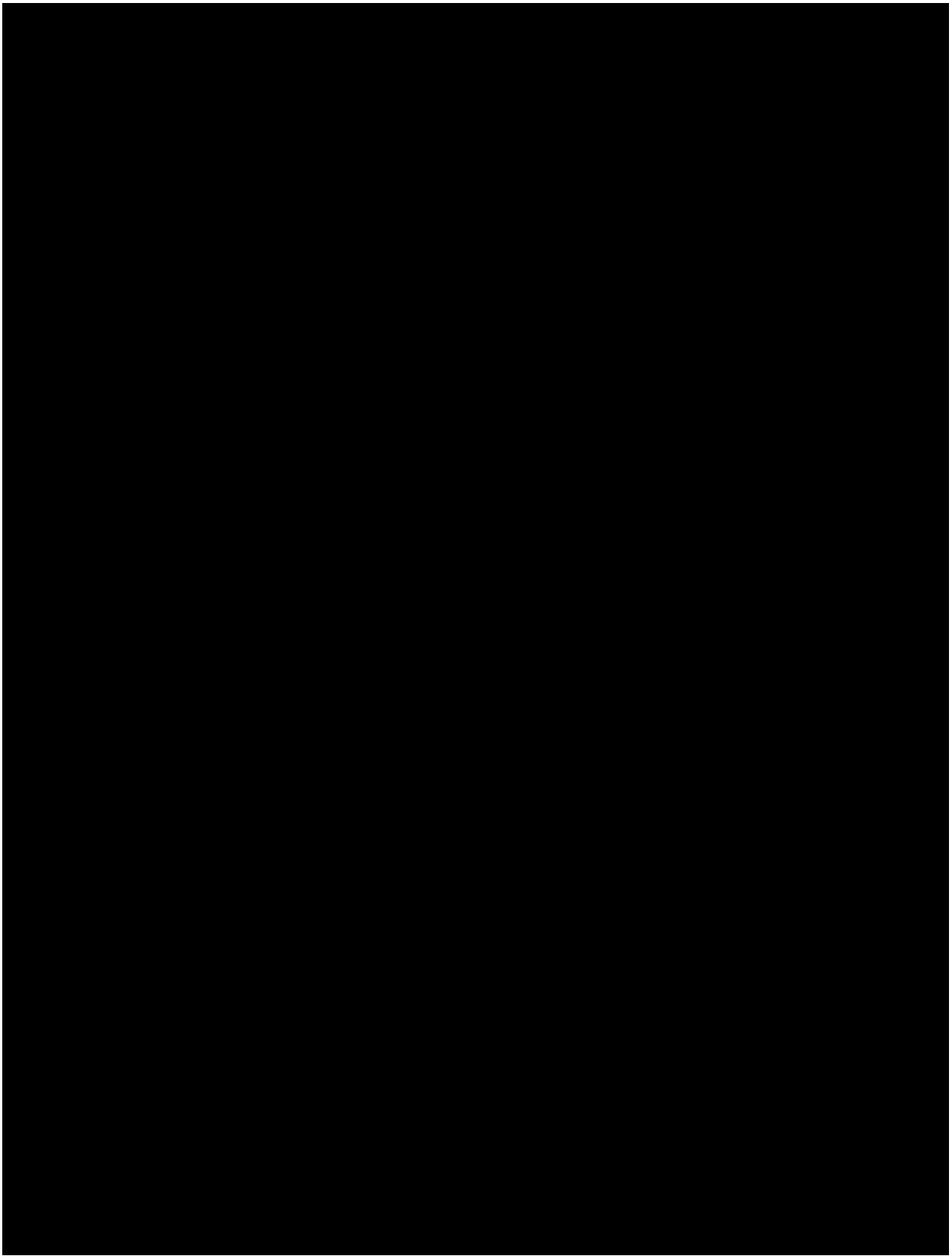
A scatter plot of baseline anti-CTL019 antibodies versus qPCR AUC0-28d and Cmax will be presented along with the appropriate regression line and equation. In addition boxplots of anti-CTL019 antibodies at enrollment by month 3 disease response will be presented. The same response categories will be used for a similar boxplot summarizing the maximum fold change of anti-CTL019 post-infusion.

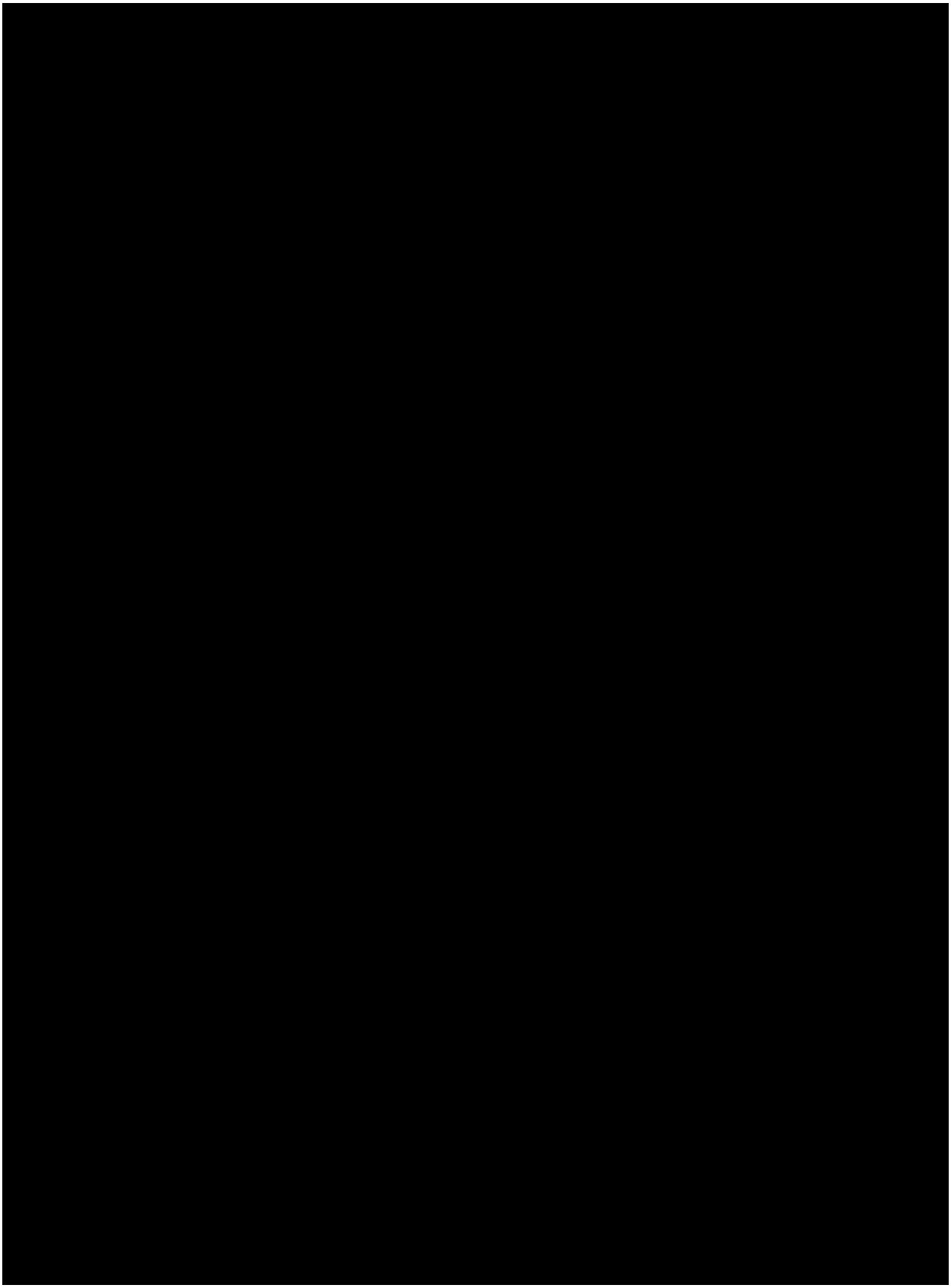
The plot of CTL019 transgene concentration-time profile will be presented by post-infusion anti-CTL019 antibody status.

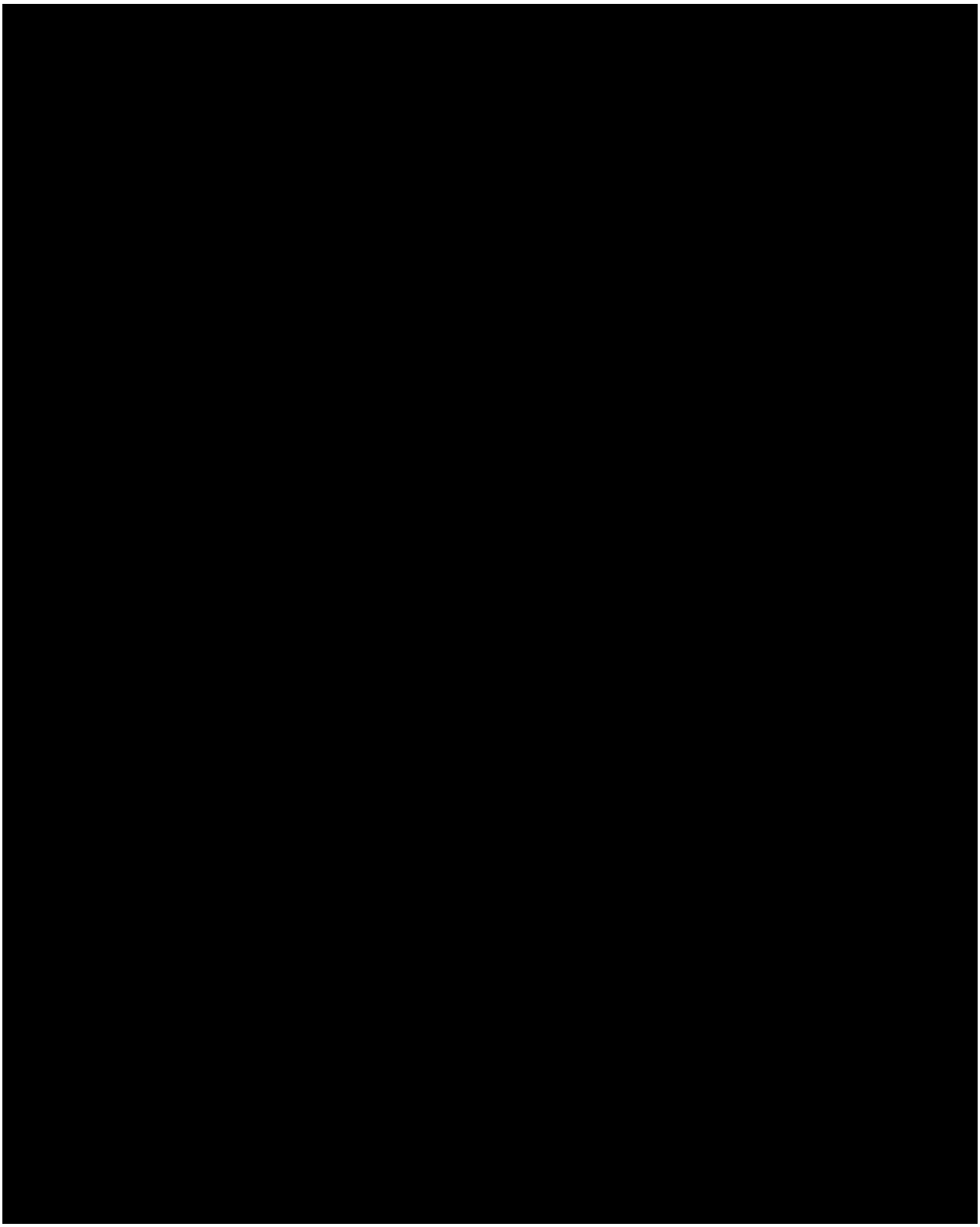
Cellular immunogenicity:

The cellular immunogenicity will be summarized by time points separated for CTL019 Pool 1 Peptides and CTL019 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.

[redacted]







4.16 Determination of sample size

In two retrospective studies in relapsed and refractory DLBCL patients receiving 2nd or 3rd line therapies, the observed ORR were 14% and 20% (Seshadri et al 2008, Elstrom et al 2010). In a recent prospective clinical trial with ibrutinib in patients who had a median of 3 prior lines of therapy, the ORR in the ABC subtype was 40% and in the GC subtype 5% leading to an overall ORR of 21.7% (Wilson et al 2012).

Based on the null hypothesis of ORR $\leq$ 20% and alternative hypothesis of ORR >20%, 80 patients in the primary analysis will provide 94% cumulative power to demonstrate statistical significance, using a 2-look Lan-DeMets group sequential design with O'Brien-Fleming type boundary and an exact CI at one-sided cumulative 0.025 level of significance, if the underlying ORR is 38%. In this setting, an ORR of 24/80=30% will be needed to claim success.

Assuming approximately 20% enrolled patients will not be infused due to reasons such as manufactory failure, worsening of patient's condition, etc., at least 100 patients need to be enrolled to ensure 80 patients are treated and hence will be used for the primary analysis. At least 25 patients in each of the GC and ABC DLBCL subtypes will be treated.

4.17 Interim analyses

One interim analysis for futility and overwhelming efficacy is planned for the study when approximately 50 patients of the planned 80 (62.5%) in main cohort have received CTL019 infusion and the last patient has completed 3 months from study day 1 infusion or discontinued earlier. An α-spending function according to Lan-DeMets (O'Brien-Fleming), as implemented in EAST 6.3, will be used to construct the efficacy stopping boundary (Lan and DeMets 1983).

Based on this choice of α-spending function, if the interim analysis is performed with 50 patients, the lower bound of the 2-sided 99.08% exact confidence interval for ORR will need to be greater than 20% to declare statistical significance. As a result, an ORR of 19/50=38% will be needed to claim success at interim analysis. The study will continue to the planned final analysis even if success is claimed at interim analysis. At the final analysis when 80 patients are treated and followed for at least 3 months, 2-sided 95.28% exact CI will be used correspondingly, requiring an ORR of 24/80=30% to claim success.

The futility stopping boundary will be determined based on the predicted probability of success at the final analysis. The study may be stopped for futility if the posterior predictive probability of claiming success at the end of the study, i.e. observing at least 24 responders out of 80 total patients, is found to be smaller than 10% based on the data from interim analysis. Based on a non-informative prior (Beta (1,1)) on the probability of success, if less than or equal to 12 responders are observed from 50 patients in the interim analysis, then the Bayesian predictive probability of observing at least 24 responders from 80 patients at the primary analysis will be less than 10%.

Only the patients who have received CTL019 infusion and followed for at least 3 months or discontinued earlier will be included in the efficacy IA analyses.

In case the actual number of patients included in the interim analysis cut-off date is not exactly equal to the planned 50 patients, the efficacy and futility boundaries will be re-calculated based on the actual number of patients using the pre-specified α-spending function and predicted probability of success criteria, respectively.

The above decision rules will be used by the DMC, to make recommendations to continue or stop the trial. The DMC will also review safety data periodically.

The scope of interim analysis is provided in Section 6.

5 Additional analysis definitions and conventions

5.1 Response rate analyses

For the analyses of response rate (e.g, ORR), the rates will be summarized along with a 2-sided 95% exact Clopper-Pearson confidence interval. Sample code is provided below.

```
PROC FREQ data=dataset;

TABLEES outcome/binomial(CL=exact);run;

/* outcome is the variable to indicate response or not, note that if the outcome is
dichotomous variable, then the proportion of outcome=0 will be calculated.*/
```

5.2 Assessment date

For each assessment (i.e. evaluation number), the **assessment date** is calculated as:

- the latest date of all radiological measurement dates (e.g. CT-scan (or MRI), and excluding both bone marrow biopsy and B-symptoms assessment), if the overall disease response at that assessment is CR/PR/SD/UNK,

- the earliest date of all measurement dates (e.g. CT-scan (or MRI), including bone marrow biopsy, but excluding B-symptoms assessments) if the overall disease response at that assessment is PD.

5.3 Time-to-event analyses

For time-to-event analyses (DOR, RFS, EFS and OS), the survival function will be estimated using the Kaplan-Meier (product-limit) method as implemented in PROC LIFETEST (see examples below). Median survival will be obtained along with 95% confidence intervals calculated from PROC LIFETEST output using the loglog option available within PROC LIFETEST, Kaplan-Meier estimates with 95% confidence intervals at specific time points will be summarized.

```
PROC LIFETEST data=dataset METHOD=KM conftype=loglog;

TIME survtime*censor(1);

RUN;

/* survtime represents variable containing event/censor times;

censor represents censoring variable (1=censored, 0=event); */
```

The time points can be expressed in weeks or in months depending on the time-to-event variable (e.g. overall survival might require a different scale than duration of response). If 'months' is used it should be noted that 1 month is defined as (365.25/12) =30.4375 days, which is not equal to 4 weeks.

In completing risk analysis, the cumulative incidence function (CIF) can be estimated following macro:

```
%CIF(data=dataset, out=est, time=survtime, status=status, event=1);

/* survtime represents variable containing event/censor times;

status represents status variable (0=censored, 1= event of interest, 2= competing
events); */
```

5.4 Duration of follow-up

For time to event endpoints (DOR, EFS and OS), the follow up time (in months) is calculated as:

Follow-up time = (Date of event or censoring – Date of first CTL019 infusion + 1)/30.4375.

The study follow up duration (in months) will be calculated as (Analysis cut-off date – Date of first CTL019 infusion + 1)/30.4375).

5.5 Time windows

In order to summarize the [redacted] PK [redacted] 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.

For PK [redacted], 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.

[redacted]

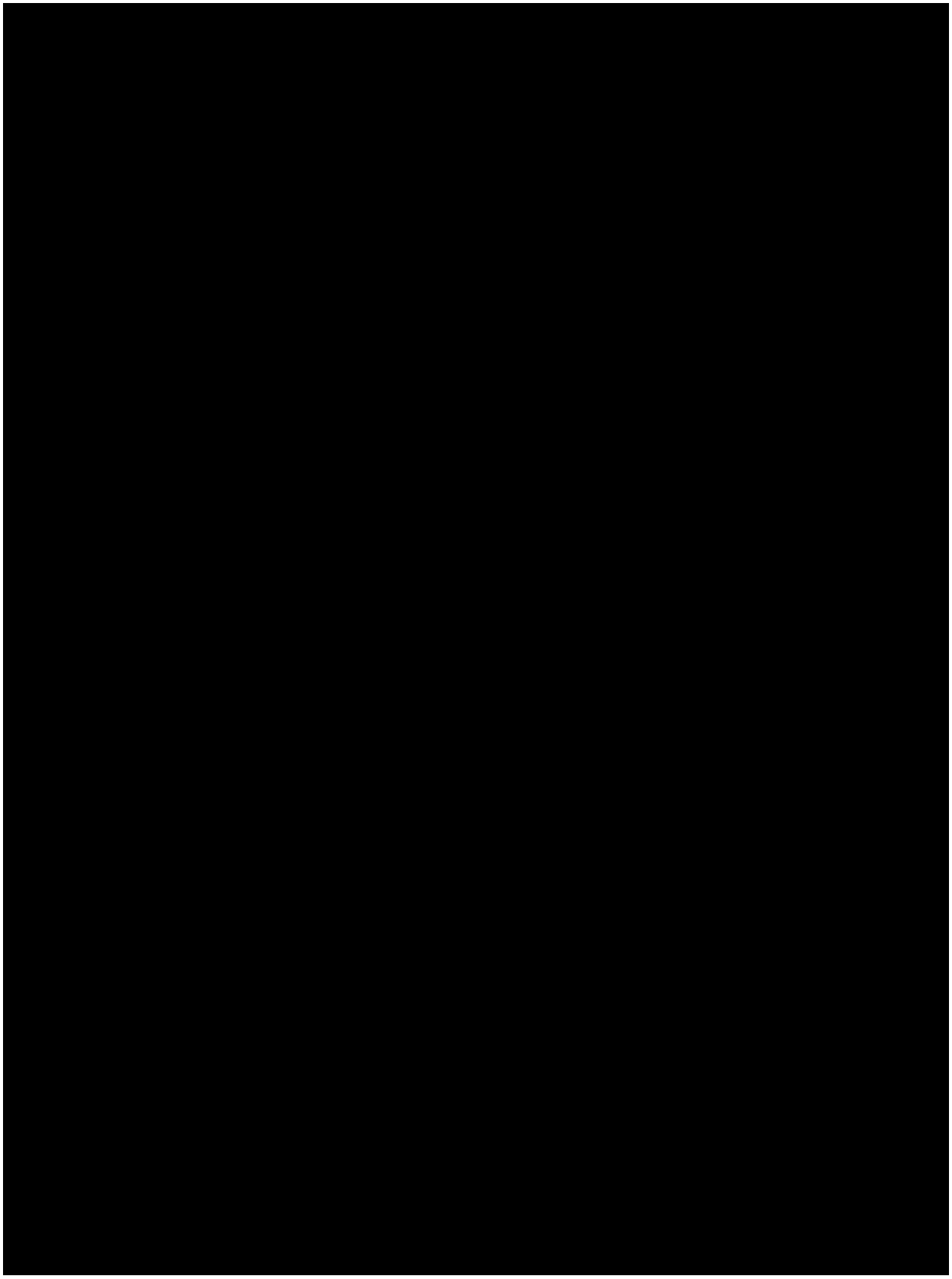


Table 5-2 shows the defined time windows for PK sample.

Table 5-2 Time windows for PK

Time Window	Planned visit timing (Study day)	Time Window Definition (Study day)
CTL019 pharmacokinetics by q-PCR in peripheral blood		
W-3 to D-8 Enrollment/Pre-Chemotherapy	Before Study Day 1	≤-1
D1 10 min ± 5 min post-infusion	1	1
D2	2	2
D4±1d	4	3 to 5
D7±1d	7	6 to 9
D11±1d	11	10 to 12
D14±1d	14	13 to 15
D17±1d	17	16 to 18
D21±3d	21	19 to 24
D28±7d	28	25 to 44
M2±14d	61	45 to 76
M3±14d	91	77 to 136
M6±14d	183	137 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 822
M30±14d	913	823 to 1004
M36±14d	1096	1005 to 1187
M42±14d	1278	1188 to 1369
M48±14d	1461	1370 to 1552
M54±14d	1644	1553 to 1734
M60±14d	1826	≥ 1735
CTL019 pharmacokinetics by flow cytometry in peripheral blood		
W-3 to D-8 Enrollment/Pre-Chemotherapy	Before Study Day 1	≤-1
D4±1d	4	1 to 5
D7±1d	7	6 to 9
D11±1d	11	10 to 12
D14±1d	14	13 to 15
D17±1d	17	16 to 18
D21±3d	21	19 to 24
D28±7d	28	25 to 44
M2±14d	61	45 to 76
M3±14d	91	77 to 136
M6±14d	183	137 to 228
M9±14d	274	229 to 319
M12±14d	365	≥ 320
CTL019 pharmacokinetics by q-PCR in bone marrow aspirate		
CTL019 pharmacokinetics by flow cytometry in bone marrow aspirate		

CTL019 pharmacokinetics by q-PCR in lymph node biopsy		
W-8 to W-4 Screening	Before Study Week -4	≤-1
M3±14d	91	60 to 136
CTL019 pharmacokinetics by q-PCR in CSF		
W-8 to W-4 Screening	Before Study Week-4	≤-1
Immunogenicity serum sample (Humoral) **Immunogenicity peripheral blood sample (Cellular)**		
W-3 to D-8 Enrollment/Pre-Chemotherapy	Before Study Day 1	≤-1
D14±1d	14	1 to 21
D28±7d	28	22 to 59
M3±14d	91	60 to 136
M6±14d	183	137 to 273
M12±14d	365	≥274

Study Day 1 = start date of CTL019

[redacted]

5.6 Handling of missing or partial dates

For patients not known to have died prior to the cut-off date:

- All events with start date before or on the cut-off date, and with end date missing or after the cut-off date will be reported as "continuing".
- This approach applies, in particular, to AEs and concomitant medication reports. For these events, the end date will not be imputed and therefore will not appear in the listings.

For patients known to have died prior to or on the cut-off date:

- All events with start date before or on the cut-off date, and with end date missing or after the cut-off date will have the end date imputed to the death date.
- This approach applies, in particular, to AEs and concomitant medication reports. For these events, the imputed end date will not appear in the listings.

5.6.1 AE date imputation

Date imputation is the creation of a new, complete date from a partial one according to an agreed and acceptable algorithm. Missing date for AE will be handled according to rules specified below. A partial date is simply an incomplete date e.g. DDOCT2001: the days are missing from this DDMMMYYYY date.

Partial AE start dates, if left partial, would ultimately mean the following:

It would not be possible to place the AE in time.

Therefore the treatment/dosage at the time of the event would be unknown.

Therefore the event could not be reported/summarized appropriately – if at all.

Therefore it is important to perform date imputation to ensure that as many data events are represented as correctly as possible. Of course partial and/or missing dates should *also* be caught as edit checks and passed back to the investigator for resolution.

The following Table 5-5 explains the abbreviations used.

Table 5-4 AE/treatment date abbreviations

	Day	Month	Year
Partial Adverse Event Start Date	<not used>	AEM	AEY
Treatment Start Date (TRTSTD)	<not used>	TRTM	TRTY

The following matrix Table 5-6 describes the possible combinations and their associated imputations. In the light grey boxes the upper text indicates the imputation and the lower text the relationship of the AE start date to the treatment start date (TRTSTD).

Table 5-5 AE partial date imputation algorithm

	AEM MISSING	AEM < TRTM	AEM = TRTM	AEM > TRTM
AEY MISSING	NC Uncertain	NC Uncertain	NC Uncertain	NC Uncertain
AEY < TRTY	(D) Before TRTSTD	(C) Before TRTSTD	(C) Before TRTSTD	(C) Before TRTSTD
AEY = TRTY	(B) Uncertain	(C) Before TRTSTD	(B) Uncertain	(A) After TRTSTD
AEY > TRTY	(E) After TRTSTD	(A) After TRTSTD	(A) After TRTSTD	(A) After TRTSTD

The following Table 5-7 is the legend to the above table.

Table 5-6 AE/treatment date relationship and imputation legend

Relationship	
Before TRTSTD	Indicates AE start date prior to Treatment Start Date
After TRTSTD	Indicates AE start date after Treatment Start Date
Uncertain	Insufficient to determine the relationship of AE start date to Treatment Start Date
Imputation Calculation	
NC / Blank	No convention/imputation
(A)	01MONYYYY
(B)	TRTSTD+1
(C)	15MONYYYY
(D)	01JULYYYY
(E)	01JANYYYY

The following Table 5-8 gives a few examples.

Table 5-7 AE imputation example scenarios

Partial AE start date	Treatment start date	Relationship	Imputation Calculation	Imputed Date
12mmyyyy	20OCT2001	Uncertain	NC	<blank>
ddmmm2000	20OCT2001	Before	(D)	01JUL2000
ddmmm2002	20OCT2001	After	(E)	01JAN2002
ddmmm2001	20OCT2001	Uncertain	(B)	21OCT2001
ddSEP2001	20OCT2001	Before	(C)	15SEP2001
ddOCT2001	20OCT2001	Uncertain	(B)	21OCT2001

Partial AE start date	Treatment start date	Relationship	Imputation Calculation	Imputed Date
ddNOV2001	20OCT2001	After	(A)	01NOV2001

Note, it may happen that the imputed AE start is after AE end date, in that case, imputed AE start=AE end date.

There **will be no** attempt to impute the following:

- **Missing** AE start dates
- AE start dates **missing the year**

Partial AE end date will be imputed as follows:

- Imputed date = min (date of death if applicable, last day of the month), if day is missing;
- Imputed date = min (date of death if applicable, 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.

Missing AE end date or AE end date after data cutoff will be imputed as follows:

All events with start date before or on the cut-off date, and with end date missing or after the cut-off date will have the end date imputed as the minimum of the cut-off date or date of death or study evaluation completion date (if applicable). For these events, the imputed end date will not appear in the listings, instead, they will be reported as "continuing".

5.6.2 Concomitant medication date imputation

The imputation of the start date and end date of concomitant medication will follow the same conventions as for AE date..

5.6.3 Incomplete date for anti-neoplastic therapies

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.

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.

5.6.4 Incomplete assessment dates for disease assessment

All investigation dates (e.g. X-ray, 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 5.2). 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.

5.6.5 Incomplete date for relapse or last known date subject in remission

The "Primary Malignancy Status" CRF will be used to track the relapse status for those patients who enter the secondary follow up phase while in remission.

If the day or month of date of relapse or last known date subject in remission is missing, it will be imputed to the minimal of date of assessment and the following:

- Missing day: 15th day of the month and year
- Missing day and month: July 1st of the year

5.6.6 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 3.1.7) 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 imputed to the maximum of the full (non-imputed) last contact date and 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

5.6.7 Incomplete date for initial diagnosis

If the day or month of initial diagnosis is missing, the date of initial diagnosis 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

5.6.8 Date of hospitalization imputation

The imputation of the start and end date of hospitalization will follow the same conventions as for AE date.

5.7 Determination of missing scheduled disease assessments

For some time-to-event endpoints (i.e. DOR, PFS, EFS), classification of censoring or event can depend on the number of missing scheduled disease assessments.

The protocol defined schedule of disease assessments is month 1, month 3, every 3 months till month 12, every 6 months till month 24, then every 12 months till month 60. Each assessment is expected to be performed at the scheduled time point plus or minus 2 weeks in general, i.e. the window is 4 weeks.

An event is considered as after 2 or more missing scheduled disease assessments if the distance between the last adequate non-PD assessment and the event is larger than the threshold, defined as two times the protocol specified interval between the disease assessments plus the protocol allowed window around the assessments.

Given the multiple different assessment frequencies, the definition of "2 or more missing scheduled disease assessments" is simplified as follows:

An event is considered as having occurred after 2 or more missing scheduled disease assessments if the distance between the last adequate non-PD assessment and the event is:

- >98 days (i.e. 14 weeks) if there is no post-baseline non-PD assessment
- >182 days (i.e. 2+3+1 months), if the last adequate non-PD assessment occurs on or before Day 45 (i.e. middle point of Month 1 and Month 3)
- >213 days (i.e. 3+3+1 months), if the last adequate non-PD assessment occurs after Day 45 and on or before Day 228 (i.e. middle point of Month 6 and Month 9)
- >304 days (i.e. 3+6+1 months), if the last adequate non-PD assessment occurs after Day 228 and on or before day 319 (i.e. middle point of Month 9 and Month 12)
- >578 days (i.e. 6+12+1 months), if the last adequate non-PD assessment occurs after Day 319 and on or before Day 456 (i.e. middle point of Month 12 and Month 18)
- >760 days (i.e. 12+12+1 months), if the last adequate non-PD assessment occurs after Day 456

6 Scope and patient population of interim, primary and final analysis

6.1 Interim analysis scope

For the interim analysis conducted when at least 50 patients had followed for 3 months or discontinued earlier, no CSR will be written. First interpretable results (FIR) will be issued for main efficacy and safety results, including

- Patient disposition
- Demographics and baseline disease characteristics
- Prior/post antineoplastic therapy, concomitant medication
- ORR, DOR, PFS, EFS for patients in EAS only and OS for all infused patients (FAS)
- Sensitivity and subgroup analysis for ORR, except for ORR on PPS.
- Bayesian predictive probability for success at primary analysis
- Dose administration
- Death and Adverse events (all AE, SAE, AESI)
- Detailed information about CRS
- Lab results (shift table and resolution of cytopenias)
- PK parameter and concentration summary
- Other safety data (vital sign)

Details can be found in interim analysis TFL shells.

6.2 Analysis population for primary and subsequent analyses

At the time of primary analysis, there are less than 15 infused patients in cohort A. No separate summary will be provided for cohort A. Patients from cohort A (Fraunhofer manufacturing) will be listed separately. Selected endpoints will be summarized for both cohorts combined as specified in Table 6-1.

Table 6-1 Endpoints, analysis population and manufacturing facilities

	Enrolled but not infused	EAS/PAS			FAS/SAF		
Endpoints	All	Main Cohort[1]	Cohort A[1]	All[1]	Main Cohort[1]	Cohort A[1]	All[1]
Disposition*	X	X					X
Demographics*	X	X					X
Baseline disease characteristics*	X	X					X
Medical History	X	X					X
Treatment*	X	X					X

Time from enrollment to disc./infusion	X	X	X
ORR (including subgroups)*		X	
DOR (including subgroups)*		X	
TTR*		X	
PFS*		X	X
EFS*		X	X
OS*		X	X
All Safety except AE			X
Adverse Event*	X		X
PK Summary*		X	
[redacted]		X	
[redacted]		X	

1. Manufacturing facility: Main Cohort=Morris Plain; Cohort A= Fraunhofer; All=all manufacturing facilities
* Key efficacy and safety endpoints.

Key efficacy and safety endpoints (marked by * in Table 6-1) in will be summarized by cohort separately as well as for both cohorts combined only after at least 15 patients in cohort A have been infused and followed for at least 3 month.

7 References

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