Adaptimmune LLC

STATISTICAL ANALYSIS PLAN

Protocol Number TCR2-21-01

Amendment Version 2.0

A PHASE 1/2 SINGLE ARM OPEN-LABEL CLINICAL TRIAL OF TC-510 IN PATIENTS WITH ADVANCED MESOTHELIN-EXPRESSING CANCER

SPONSOR

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FINAL Version 1.0

SIGNATURE PAGE

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VERSION HISTORY			
Version	**Version Date**	**Summary of Changes**	**Rationale**
1.0	28 February 2025	Original	

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List of Abbreviations and Definition of Terms

Abbreviation	Description
ADAP	Adaptimmune
AE	Adverse Event
AESI	Adverse Event of Special Interest
ATC-3	Anatomical Therapeutic Chemical 3rd level
BMI	Body Mass Index
BOR	Best Overall Response
CI	Confidence Interval
CR	Complete Response
CRP	C Reactive Protein
CRS	Cytokine Release Syndrome
aCSR	Abbreviated Clinical Study Report
CTCAE	Common Toxicity Criteria for Adverse Events
DCR	Disease Control Rate
DNA	Deoxyribonucleic acid
DoR	Duration of Response
DPP	Data Presentation Plan
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
FDA	Food and Drug Administration
ICH	International Council for Harmonisation
IFNg	Interferon gamma
IL-6	Interleukin-6
IO	Immuno-oncology

iRECIST	Immune-based Response Evaluation Criteria in Solid Tumors
ITT	Intention-to-Treat
LLN	Lower Limit of Normal
LTFU	Long-Term Follow-Up
LYM	Lymphocytes
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intention-to-Treat
MPM	Malignant pleural/peritoneal mesothelioma
MSLN	Mesothelin
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
NE	Not Evaluable
NEUT	Neutrophils
NSCLC	Non-small cell lung cancer
PD-L1	Programmed Cell Death Ligand 1
PLAT	Platelets
ORR	Overall Response Rate
OS	Overall Survival
PD	Progressive Disease
PFS	Progression Free Survival
PLAT	Platelets
PR	Partial Response
PT	Preferred Term
RCL	Replication Competent Lentivirus
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended Phase 2 Dose
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan

SD	Stable Disease
SRT	Safety Review Team
SOC	System Organ Class
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
TFL	Tables, Figures and Listings
TNF-a	Tumor necrosis factor alpha
TTR	Time to Response
ULN	Upper Limit of Normal
WBC	White Blood Cells
WHO	World Health Organization

1 Introduction

The purpose of this statistical analysis plan (SAP) is to document technical and detailed specifications for the efficacy and safety analyses of data collected for study protocol TCR2-21-01 (up to and including Version 2.0 (29Mar2023)) [investigational product: TC-510]. Due to early termination of the study prior to reaching any analysis milestones, this SAP will describe analyses to be incorporated into an abbreviated Clinical Study Report (aCSR), and will only constitute reporting of a subset of the endpoints outlined in the study protocol.

The aCSR will be based on the database lock for the planned primary analysis. Data will continue to be collected outside of the database for subjects still in long-term follow-up, which will then be added as an addendum to the aCSR for final reporting (once all subjects have completed the study).

A final SAP should be in place prior to the database lock, and any deviations from the SAP post database lock, or unplanned analyses performed, will be clearly identified in the aCSR. This SAP is based upon Section 14 (Statistical and Data Analysis) of the trial protocol and is prepared in compliance with the International Council for Harmonisation (ICH).

2 Objectives

2.1 Phase 1 Objectives

2.1.1 Primary Objectives

- To evaluate the safety of autologous genetically modified TC-510 in patients with MSLN-expressing metastatic or unresectable solid tumors.
- Establish the recommended phase 2 dose (RP2D) according to dose-limiting toxicity (DLT) of defined adverse events.

2.1.2 Secondary Objectives

- To determine the overall response rate (ORR) (complete response [CR] + partial response [PR]) according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 and duration of response (DoR).
- To determine the disease control rate (DCR), defined as a composite of ORR and stable disease (SD) lasting at least 8 weeks.
- To evaluate the survival benefit of autologous genetically modified TC-510 as assessed by progression-free survival (PFS) and overall survival (OS)
- To assess humoral immunogenicity to TC-510

2.2 Phase 2 Objectives

2.2.1 Primary Objective

- To evaluate the safety of autologous genetically modified TC-510 in patients with MSLN-expressing metastatic or unresectable solid tumors.
    - Endpoints: ORR (CR + PR) and DCR (ORR + SD ≥ 8 weeks) according to RECIST v 1.1.

2.2.2 Secondary Objectives

- To evaluate the efficacy of autologous genetically modified TC-510 in patients with MSLN-expressing unresectable, metastatic, or recurrent cancers as assessed by TTR, DoR, PFS, and OS.
- To further evaluate the safety of autologous genetically modified TC-510.
- To assess whether patients experience a response upon subsequent TC-510 infusion(s).

2.2.3 Exploratory Objectives (Phase 1 and 2)

- To evaluate TC-510 expansion, persistence, and cytokine production in vivo.
- To evaluate key TC-510 product attributes pre- and post-infusion (e.g., phenotype, functionality).
- To evaluate TC-510 infiltration in tumor tissue.
- To evaluate the correlation of metabolic activity of target and non-target lesions post TC-510 infusion and clinical activity.
- To evaluate immune markers in the tumor microenvironment (e.g., PD-L1 expression) before and after TC-510 infusion and their correlation with toxicity and response.
- To evaluate the changes in health-related quality of life following treatment with TC-510 (only Phase 2).
- To evaluate the response to TC-510 by iRECIST

3 Study Overview

3.1 Study Design

The study design for phase 1 is a modified 3+3 dose escalation strategy with varying TC-510 doses preceded by lymphodepletion chemotherapy. Once the RP2D is identified, additional patients may be treated at the RP2D in an expansion cohort. In the Phase 2 portion of the study, patients will receive TC-510 at the RP2D and will be stratified according to their cancer diagnosis in 7 cohorts: malignant pleural/peritoneal mesothelioma (MPM), serous ovarian adenocarcinoma, pancreatic adenocarcinoma, colorectal cancer, triple negative breast cancer, non-small cell lung cancer (NSCLC), and cholangiocarcinoma.

Refer to Section 5 of the study protocol for further details of the study design.

3.2 Treatments

3.2.1 Premedication

Please refer to Section 7.1 and 7.3 of the study protocol for details on leukapheresis and lymphodepleting chemotherapy respectively.

3.2.2 TC-510 Infusion

Please refer to Section 7.4 of the study protocol for details.

3.2.4 TC-510 Retreatment

Subjects may be eligible for retreatment with TC-510 in the Phase 1 RP2D expansion cohort, or in the Phase 2 portion of the study. Please refer to Section 9.4 of the study protocol for further details.

3.3 Determination of Sample Size

Details provided below on sample size are as per the original protocol design.

The Phase 1 study design is a modified 3+3 dose escalation strategy, recruiting in cohorts of 3 which can be expanded to 6 patients in total according to the decision rules of the design. Once the RP2D is identified, up to 10 patients may be subsequently treated at the RP2D in an expansion cohort to further delineate the toxicity profile of TC-510 prior to advancing to the Phase 2 portion of the study. Approximately 25-30 patients will be treated in the Phase 1 portion of the study, however the final number will depend on how many dose levels are explored to determine the RP2D, and the number of subjects recruited to the RP2D expansion cohort (if any). Further details of the dose escalation schema can be found in sections 5 and 12 of the study protocol.

In phase 2 a total of 20 patients will be treated with single agent TC-510 in each one of the 7 cancer diagnosis cohorts. Up to approximately 140 patients will be treated in the phase 2 portion of the study. TC-510 will be considered for further development if there is at least 1 response in a disease cohort. For each planned Phase 2 cohort, 20 patients

will have an 98% probability of having at least 1 response if the true response rate is p_A = 0.2.

Due to the study terminating early prior to determination of the RP2D, recruitment to Phase 1 was not completed with only 6 patients dosed at the initial dose DL0, and Phase 2 was never initiated.

4 Study Endpoints and Covariates

4.1 Study Endpoints

The primary and secondary endpoints associated with study objectives for Phase 1 is summarized in table 1 below, and marked whether they are in scope for this SAP and aCSR. Reporting of all exploratory endpoints will be handled outside of the aCSR reporting specified in this SAP. Phase 2 study objectives are not applicable as the Phase 2 portion of the study was never initiated.

Table 1. Phase 1 Endpoints

Objective	Endpoint	Type of Endpoint	In Scope for SAP	In Scope for aCSR
To evaluate the safety of autologous genetically modified TC-510 in patients with MSLN-expressing metastatic or unresectable solid tumors.	See section 14.3.4.1 of the study protocol for details of safety analyses.	Primary	Yes	Yes
Establish the recommended phase 2 dose (RP2D) according to dose-limiting toxicity (DLT) of defined adverse events.	Establish the RP2D according to DLT of defined AEs	Primary	No	Yes
To determine the overall response rate (ORR) (complete response [CR] + partial response [PR]) according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 and duration of response (DoR).	ORR	Secondary	Yes	Yes
	DoR	Secondary	No	No

Objective	Endpoint	Type of Endpoint	In Scope for SAP	In Scope for aCSR
To determine the disease control rate (DCR), defined as a composite of ORR and stable disease (SD) lasting at least 8 weeks.	DCR	Secondary	Yes	Yes
To evaluate the survival benefit of autologous genetically modified TC-510 as assessed by progression-free survival (PFS) and overall survival (OS)	PFS	Secondary	No	No
	OS	Secondary	No	No
To assess humoral immunogenicity to TC-510	Humoral immunogenicity to TC-510	Secondary	No	No

4.2 Covariates

No analysis modelling is planned to be carried out for this study

5 Hypotheses

No formal hypothesis testing will be conducted.

6 Definitions

6.1 General Definitions

The definitions of baseline and study visit will supersede any definitions of the following items provided in the protocol.

6.1.1 Baseline Definition

Baseline is defined as the last non-missing assessment (including unscheduled assessments) prior to the lymphodepleting chemotherapy that preceded the TC-510 infusion.

6.1.2 Study Day Definition

Nominal study day is relative to TC-510 infusion. Day 1 and Study Day are defined in Table 2 below.

Table 2. Definition of Study Day 1 and Study Day

Day 1	The first day of the TC-510 infusion in the study
Study Day	(Date of Interest - Date of TC-510 infusion) + 1 If Date of Interest is ≥ TC-510 infusion date
	Date of Interest - Date of TC-510 infusion If Date of Interest is < TC-510 infusion date

Note: Study day has been redefined here as Day 1 for TC-510 infusion, whereas it is Day 0 in the protocol.

6.1.3 Treatment Group Definition

As there was only a single arm in the Phase 1 portion of the study, and all dosed subjects received the initial dose DL0, there will be no separate presentation of treatment groups and dose levels in this SAP. All outputs will include a single overall summary of all subjects in the respective analysis population.

6.2 Definition for Safety Endpoints

6.2.1 AEs

Refer to Section 10 of the study protocol for relevant information.

7 Analysis Population

The primary population of interest will be the modified intention-to-treat (mITT) population. The intention-to-treat (ITT) population will be used where appropriate. The DLT evaluable set will not be used for reporting in this SAP. See section 10 of the SAP for details of which analysis populations will be used for individual displays.

7.1 Intention-to-Treat (ITT)

This is the population of all subjects who sign the pre-screening informed consent form and undergo leukapheresis. Patients are considered to be enrolled on the study upon completion of a successful leukapheresis procedure. The ITT population will predominantly be used for listings, and specific summary displays where appropriate (see SAP section 10 for details).

7.2 Modified Intention-to-Treat (mITT)

This is the population of all enrolled subjects who received at least one TC-510 infusion. The mITT definition specified here agrees with the protocol stated safety set, and differs to the protocol specified mITT definition as any dose of TC-510 is acceptable, not only the planned dose.

8 Interim Analysis and Data Review

8.1 Interim Analysis

No formal interim analysis of study endpoints is planned to be performed in this study. However a safety review team (SRT) will be used as described in section 8.2.

8.2 Data Review

A Safety Review Team (SRT) will perform ongoing comprehensive evaluation of the safety profile for the TC-510 product, including routine periodic reviews of available safety data. The SRT is specifically chartered to review safety and efficacy data during phase 1 of the study and make a recommendation to progress the study from phase 1 to

phase 2 based on the incidence of TC-510 DLTs and review of SAEs. SRT input was not required for phase 2 due to early termination of the study.

9 General Analysis Conventions

Data collected in this study will be analyzed using summary tables, figures/plots or subject data listings. Unscheduled assessments associated with non-protocol clinical visits or obtained in the course of investigating or managing adverse events will be included in listings, but not summaries. If there is more than one laboratory value available for a given post-baseline visit, the worst laboratory value (to be identified by parameter if worst equals a high or low value) will be used in summaries and all observations will be presented in listings, unless otherwise stated.

Continuous variables will be summarized using descriptive statistics (Number of subjects, Mean, Median, Standard deviation, Minimum and Maximum). Continuous data that are expected to be skewed will be presented in terms of the maximum, upper quartile, median, mean, lower quartile, minimum, standard deviation, and number of observations. The minimum and maximum will be reported to the same number of decimal places as the raw data recorded in the database. The mean, median, lower quartile and upper quartile will be reported to one more decimal place than the raw data recorded in the database. The standard deviation will be reported to two more decimal places than the raw data recorded in the database. In general, the maximum number of decimal places reported shall be four for any summary statistic. Confidence intervals (CIs) will be presented to one more decimal place than the raw data. If the confidence intervals are calculated for proportions, then they will be presented to three decimal places.

Categorical variables will be summarized in terms of the number of subjects providing data at the relevant time point (n), frequency counts and percentages. Percentages will be displayed to one decimal place. Any planned collapsing of categories will be detailed in the SAP text and the data displays.

Adverse events and medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 24.0. Prior and concomitant medications will be coded to World Health Organization (WHO) Drug B3 Global, March 2021.

All tables, listings, and figures will be programmed using SAS Version 9.4 or higher. A mock shell document will be produced providing both a table of contents list for the TFLs to be produced for use in the aCSR, and template shells will be provided as needed. This may be expanded into a Data Presentation Plan (DPP) if further reporting details are required to be specified.

9.1 Study Periods

For all safety summaries/listings, data will be presented during the period from start of lymphodepleting chemotherapy to the end of the interventional phase unless otherwise stated. This period will be stated in display titles where it applies.

9.2 Visit Windows

Study visits are expected to occur according to the protocol schedule. All data will be tabulated per the evaluation visit as recorded on the eCRF even if the assessment is outside of the visit window. No imputation of data will be performed for missed assessments unless otherwise noted. In data listings (where relevant), the relative study day of all dates will be presented.

10 Statistical Methods of Analysis

10.1 Handling of Dropouts or Missing Data

In general, imputed partial dates will not be used to derive study day, duration (e.g., duration of adverse events), or elapsed time variables. Imputed dates will not be used for deriving the last contact date.

Imputed dates will not be displayed in listings unless otherwise stated.

Imputing partial start dates for AEs, initial diagnosis, and prior/concomitant medications:

a) If the year is unknown, the date will not be imputed and will be assigned a missing value.
b) If only year is present, and month and day are unknown, then:
    1. If the year matches the first dose date of lymphodepleting chemotherapy:
        - If the stop date is available and complete and is on or after the first lymphodepleting chemotherapy date, then impute to the month and day of the first lymphodepleting chemotherapy date.
        - If the stop date is available and complete, and is before the first lymphodepleting chemotherapy date, then impute to the first day of the month of the stop date.
        - If the stop date is missing (and unable to be imputed) or no stop date is applicable, then impute to the month and day of the first lymphodepleting chemotherapy date.
    2. Otherwise, assign ‘January 01’.
c) If month and year are present and the day is unknown, then:
    1. If the month and year match the first lymphodepleting chemotherapy date, then impute to the day of the first lymphodepleting chemotherapy date.
    2. Otherwise, assign ‘01’ of the month.

Imputing partial AE and prior/concomitant medication stop dates:

a) If the year is unknown, the date will not be imputed and will be assigned a missing value.
b) If the month is unknown, then assign 'December 31'.
c) If the day is unknown, then impute to the last day of the month.

Note: After imputation, if the imputed date is later than the date of death or the date that the subject ends the study, then the date of death or date of end of the study will be used, whichever is earlier. If AE is ongoing but the subject discontinues the study, then the stop date will be resolved to the date that the subject discontinues the study.

If a period determination cannot be made for an adverse event, it will be attributed to the phase between lymphodepletion and end of interventional phase.

10.2 Pooling of Centers in Multi-Center Studies

Endpoint data will not be summarized by study center.

10.3 Multiple Comparisons/Multiplicity

No adjustments for multiple comparisons or multiplicity are planned.

10.4 Examination of Subgroups

No subgroup analyses will be conducted.

10.5 Subject Disposition

Disposition of all subjects who are enrolled onto the study (ITT) will be provided. Screening disposition data will not be summarized. Summaries of subject disposition for the ITT population will be displayed using the following columns: Dosed, Not Dosed, Overall. The "Dosed" column will include subjects who received TC-510 infusion, with

the “Not Dosed” column including all subjects who were leukapheresed but did not receive TC-510 infusion. The following data will be provided:

- Number and percentage of subjects who received Leukapheresis
- Number and percentage of subjects who received Lymphodepletion Chemotherapy
- Number and percentage of subjects who received at least one TC-510 infusion.
- Number and percentage of subjects who completed the interventional phase as well as the status at the end of the interventional phase.
- Number and percentage of subjects who completed the study as well as their status at completion.

Disposition data will be provided in a by-subject listing for all ITT subjects.

10.6 Protocol Deviations

The reporting of protocol deviations will be handled outside of this SAP (clinical activity) but will be discussed within the aCSR.

10.7 Demographic and Baseline Characteristics

The following demographic and baseline characteristics will be summarized (mITT) and listed (ITT):

- Age at time of pre-screening informed consent
- Sex (Male, Female)
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Not Reported, Unknown, Other)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not Reported)
- Primary Cancer Diagnosis/Tumor Type
- Histological Grade at Diagnosis

- Stage at Time of Diagnosis
- Time from Initial Diagnosis to Leukapheresis (months)
- Time from Initial Diagnosis to T-Cell Infusion (months)
- Prior Lines of Systemic Therapy (as a continuous variable)
- Prior Lines of Systemic Therapy categorization (0, 1, 2, 3, 4+)
- Bridging therapy (Yes, No)
- Baseline Eastern Cooperative Oncology Group (ECOG) performance

Age will be reported as the number of complete years at the date of pre-screening informed consent as collected on the eCRF.

For the mITT population, MSLN expression parameters will be listed.

10.8 Medical History

Medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 24.0. A by-subject listing of all medical history terms will be created for the mITT population.

10.9 Prior Anticancer Therapy

Asummary of prior anticancer therapy will be created displaying the number of subjects in the mITT population who received each of the following:

- Any prior anti-cancer therapy
- Prior systemic therapy
- Prior radiotherapy
- Prior cancer-related surgery
- Prior other local therapy

Additionally, separate by-subjects listings of each prior anti-cancer therapy type will be produced.

10.10 Efficacy Analysis

Efficacy analyses will be summarized for the mITT population for Phase 1 only, as the Phase 2 portion of the study was not initiated.

Analyses/displays will be produced separately based on RECIST v1.1 data from two different sources:

- By investigator assessment (EDC)
- By independent reviewer's assessment.

Note that for both investigator assessment and independent reviewer's assessment analyses, only RECIST v1.1 will be reported (no reporting of iRECIST or mesothelioma-specific RECIST). For independent reviewer's assessment, overall response for each visit is assessed by "Reader 1" and "Reader 2" independently, and the assessment chosen for analysis will be the one that has been endorsed by adjudication. If adjudication is not required, Reader 1's assessment will be chosen for analysis.

10.10.1 Objective Response Rate (ORR)

The secondary endpoint is ORR, defined as a subject having a confirmed complete response (CR) or confirmed partial response (PR) per RECIST v1.1, to be reported on the mITT population.

For investigator-assessed response, ORR will be based on programmatically determined confirmed (tumor) responses per RECIST v1.1 criteria.

For independent reviewer's assessment of response, only visit-level overall response is included in the provided raw data set to be used for reporting. Hence, other aspects (BOR, ORR, DCR) will be derived from these overall responses programmatically according to the same conventions used for investigator-assessed response.

Subjects with an unknown or missing response will be treated as non-responders (i.e., they will be included in the denominator when calculating the proportion). This includes subjects who die or discontinue the study early prior to any response assessments.

Subjects who receive any subsequent anticancer therapy (as captured on the Subsequent Anti-Cancer Therapy eCRF) post-TC-510 infusion and prior to a confirmed response being observed will be treated as non-responders.

The number and percentage of subjects achieving confirmed CR or PR will be summarized, along with the associated Wilson and Clopper-Pearson exact 2-sided 80% and 95% confidence intervals.

10.10.2 Disease Control Rate (DCR)

The secondary endpoint DCR is defined as the ORR plus the proportion of patients with SD for at least 8 weeks, to be reported on the total number of subjects in the mITT population.

To meet the criteria of SD for at least 8 weeks, a subject must have had an overall response of SD on study day ≥55 (week 8 assessment on study day 57 minus 2-day window) without prior PD.

Similar to ORR, overall response will be programmatically calculated based on investigator-assessed target/non-target tumor measurements. For independent reviewer's assessment, overall response at each visit is as per section 10.10.1, but DCR will be programmatically derived based on the above conventions.

Subjects who receive any subsequent anticancer therapy (as captured on the Subsequent Anti-Cancer Therapy eCRF) post-TC-510 infusion and prior to disease control criteria being met will be considered to have not met disease control criteria.

The number and percentage of subjects meeting criteria of disease control will be summarized, along with the associated Wilson and Clopper-Pearson exact 2-sided 80% and 95% confidence intervals.

10.10.3 Best Overall Response (BOR)

The best overall response is defined as the best response from the date of first TC-510 infusion until disease progression. Response categories from best to worst are: confirmed CR, confirmed PR, SD, PD, and NE per RECIST v1.1.

Measurements collected on the eCRFs for target, non-target, and new lesions will be used for the derivation of overall response for each visit and across all visits to determine BOR. The date of the overall response assessment is the earliest date for imaging of target, non-target and new lesions of images taken at that response assessment.

To confirm CR or PR, changes in tumor measurements must be confirmed by repeat assessments that should be no less than 4 weeks (28 days) after the criteria for response are first met, excluding the day of the initial assessment of CR or PR.

The determination of stable disease must be at least 4 weeks (study day ≥29) from the TC-510 infusion to qualify a SD as the BOR. If a subject did not have confirmed CR or PR and had stable disease for less than 4 weeks, BOR will depend on the subsequent assessments. For example, if SD is followed by a PD as the second assessment but the SD does not meet the minimum duration (4 weeks), then the BOR should be PD. Subjects who are lost to follow-up after the first SD that is obtained less than 4 weeks from the TC-510 infusion should be considered not evaluable (NE) for BOR. A missing assessment at a time point will be assigned a value of NE.

To account for potential pseudo progression, no tumor assessments prior to the 29-day window from TC-510 infusion (study day <29) will be considered for BOR determination, unless there is unequivocal progression of existing non-target lesions and/or the appearance of new malignant lesions.

In the absence of unequivocal progression of existing non-target lesions and/or the appearance of new malignant lesions:

- Overall response for any tumor assessment on or after 29-day window will be presented.
- If a subject only has tumor assessments prior to the 29-day scheduled visit, or does not have any tumor assessments in the window as of the data cutoff date, then BOR = NE.

BOR will be summarized by the number and percentage of subjects with each category of best overall response within the same summary displays as ORR and DCR, for both investigator assessment and independent reviewer's assessment. For DCR, subcategories of SD of <8 weeks and ≥8 weeks will be presented to indicate the number and percentage of subjects with BOR=SD who met criteria for disease control.

For investigator assessment, a by-subject listing will also be provided to include, but not limited to, tumor assessment date, lesion ID, lesion type, lesion location, diameters, sum of diameters of target lesions (mm), baseline sum of diameters of target lesions (mm), % change from baseline in sum of diameters, nadir (mm), % change from nadir, new lesion, investigator's overall response, derived overall response, BOR and a disease control flag. If not all target lesions were measured compared to baseline at a particular visit, sum of diameters of target lesions (mm), % change from baseline in sum of diameters, nadir (mm) and % change from nadir will not be provided as these parameters will not be applicable.
For independent reviewer's assessment, a by-subject listing will be provided to include the same data as for investigator assessment, except for baseline sum of diameters, % change from baseline sum of diameters, nadir (mm) and % change from nadir, as these parameters are not provided and not required to be calculated.

10.11 Safety Analysis

The safety assessments include study drug exposure, adverse events and clinical laboratory parameters. All safety summaries and analyses will be based upon the mITT population. Safety data will be included in data listings.

10.11.1 Study Drug Exposure

The total number of transduced T-cells will be summarized. This total dose will be programmatically calculated by summing the doses of the individual bags and will be reported as stated in the protocol in units of 10^6.

All dose administration data will be listed including:

- Cyclophosphamide dose (mg) and dose date
- Fludarabine dose (mg) and dose date
- T-cell infusion (10^6) (total number of transduced cells by bag) and dose date/time

10.11.2 Adverse Events

Adverse events (AE) will be coded by system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA) Version 24.0. Adverse events will be graded according to the NCI CTCAE v5.0.

A treatment-emergent adverse event (TEAE) in the interventional phase is defined as an AE that:

- Has an AE onset on or after the time of start of lymphodepleting chemotherapy

  Or
- For an ongoing AE which started prior to the start of lymphodepleting chemotherapy, the AE subsequently worsened (in severity grade/relationship or seriousness) after the time of starting lymphodepleting chemotherapy.

All treatment-emergent adverse event summaries will be produced for the period from start of lymphodepleting chemotherapy up until the end of the interventional phase.

Summaries of all TEAEs and TESAEs will be produced, regardless of causality and relationship to each study treatment (separate summaries for Cyclophosphamide, Fludarabine, and TC-510 infusion). Treatment-related TEAEs are those with Investigator's reasonable causality to a study drug or lymphodepleting chemotherapy marked as "definitely related", "probably related", "possibly related", or relationship is missing on the eCRF. TEAEs with an outcome of death are those with a grade of 5 or an outcome of "fatal". Additional focused summaries will be produced; see below for the full details on those to be produced.

The primary endpoint of the phase 1 portion of the study was to determine the R2PD based on DLTs observed through the dose escalation schema. No programmatical outputs will be created on DLTs, however it will be handled outside of this SAP and discussed within the aCSR.

No summaries of LTFU AEs will be produced. LTFU AEs may still be discussed within the aCSR.

10.11.2.1 Overview of Adverse Events

An overall presentation of AE information will include the following:

- Number and percentage of subjects with at least one TEAE
- Number and percentage of subjects with any TEAEs of grade ≥3
- Number and percentage of subjects with any TEAEs related to Lymphodepletion chemotherapy or TC-510 infusion
- Number and percentage of subjects with any TEAEs related to TC-510 infusion
- Number and percentage of subjects with any TEAEs related to Lymphodepletion chemotherapy or TC-510 infusion of grade ≥3

- Number and percentage of subjects with any TEAEs of grade ≥3 related to TC-510 infusion
- Number and percentage of subjects with any TESAEs
- Number and percentage of subjects with any TESAEs of grade ≥3
- Number and percentage of subjects with any TESAEs related to Lymphodepletion chemotherapy or TC-510 infusion
- Number and percentage of subjects with any TESAEs related to TC-510 infusion
- Number and percentage of subjects with any TESAEs related to Lymphodepletion chemotherapy or TC-510 infusion of grade ≥3
- Number and percentage of subjects with any TESAEs of grade ≥3 related to TC-510 infusion
- Number and percentage of subjects with any TESAEs with Fatal Outcome

10.11.2.2 Adverse Events

TEAEs will be presented by NCI CTCAE severity grade and by relationship to study treatment. If a subject had more than one occurrence of an AE, the most severe grade/strongest relationship (for aspect being reported) will be used in the summary tables. Counts will be by subject, not by event, and subjects are only counted once within each SOC or PT according to maximum CTCAE grade reported for the specified AE.

The following summaries will be provided:

- Number and percentage of subjects for each TEAE, categorized by toxicity grade and preferred term
- Number and percentage of subjects for each TEAE, categorized by toxicity grade and preferred term, and relationship
- Number and percentage of subjects for each TESAE, categorized by toxicity grade and preferred term
- Number and percentage of subjects for each TESAE, categorized by toxicity grade and preferred term, and relationship

Note: Where 'Relationship' summarization is stated, this corresponds to separate reporting for each of relationship to Cyclophosphamide / Fludarabine / TC-510 (where applicable).

A by-subject listing of all TEAEs in the period from start of lymphodepleting chemotherapy up to the end of interventional phase will be provided. This listing will include:

- subject identifier
- age
- sex
- race
- tumor type
- adverse event (SOC and PT)
- AE start date (date of onset) and study day start
- AE end date (date of resolution) and study day end
- ongoing indicator
- CTCAE grade, seriousness (Y/N), relatedness (to Cyclophosphamide, Fludarabine and TC-510)
- AE outcome

An additional by-subject listing of all AEs before start of lymphodepletion chemotherapy will be provided for the ITT population. For partially missing dates, imputation will be done according to Section 10.1. In general, however, adverse events will be assumed to be treatment-emergent unless there is clear evidence (through comparison of partial dates) to suggest that the adverse event started prior to the date of lymphodepleting therapy and did not worsen.

10.11.2.3 Adverse Events of Special Interest

Cytokine Release Syndrome (CRS)

Time to first cytokine release syndrome (CRS) will be summarized by the mean, standard deviation, median, min and max, for the subjects whose first CRS event occurred between lymphodepletion chemotherapy and end of interventional phase.

- Time to first CRS (in days):
    - If date of first occurrence of CRS ≥ T-Cell Infusion date, then Time to first CRS (in days) = date of first occurrence of CRS – date of TC-510 infusion + 1
    - If date of first occurrence of CRS < T-Cell Infusion date, then Time to first CRS (in days) = date of first occurrence of CRS – date of TC-510 infusion

Time to resolution of cytokine release syndrome (CRS) will be summarized by the mean, standard deviation, median, min and max, for the events which occurred between lymphodepletion chemotherapy and end of interventional phase.

- If a subject has only one occurrence of Cytokine Release Syndrome, then Time to resolution of CRS (in days) = [Stop date of CRS – Start date of CRS + 1]
- If a subject has multiple occurrences of Cytokine Release Syndrome, then Time to resolution of CRS (in days) is the number of days from the first onset of CRS syndrome to the last stop date of CRS, with the non-event date(s) in between subtracted. If multiple events cross over on the same day, then the day is only counted once in the total.

For events that are ongoing, the end date will be set to the last contact date. Events with partial dates will not be included.

Tocilizumab and Corticosteroid use will be summarized overall and by CRS toxicity grade. If a subject has multiple occurrences of CRS and Tocilizumab/Corticosteroids was administered for all occurrences, then only the worst will be presented in the table. If a subject has two occurrences of CRS with grades 1 and 2 and Tocilizumab/Corticosteroids

was administered for CRS with only Grade 1 then CRS with Grade 1 will be presented in the table.

A by-subject listing of CRS will be provided for all CRS events that occurred in the study for the mITT population.

Neurotoxicity

For the purposes of programmed outputs, a neurotoxicity AE includes all PTs within the SOCs of nervous system disorders or psychiatric disorders. Time to first neurotoxicity event will be summarized for the subjects whose first neurotoxicity event occurred between lymphodepletion chemotherapy and end of interventional phase. The first neurotoxicity event will be the first event with a full start date (partial dates that have been imputed will not be used).

- Time to first neurotoxicity AE (in days):
    - If First Neurotoxicity AE date ≥ T-Cell Infusion date, then Time to first neurotoxicity AE (in days) = First Neurotoxicity AE date – T-Cell Infusion date + 1.
    - If First Neurotoxicity AE date < T-Cell Infusion date, then Time to first neurotoxicity AE (in days) = First Neurotoxicity AE date – T-Cell Infusion date.

An additional summary of the total number and percentage of subjects with neurotoxicity AEs by PT will be presented, for the period from start of lymphodepletion chemotherapy up to the end of the interventional phase.

10.11.2.4 On-study Deaths

On-study deaths will be summarized by reporting number and percentage of subjects on study who died and the number and percentage of subjects who are alive at last contact with follow up ongoing, or alive at last contact but lost to follow up/withdrawn. Reason for death will be summarized. Number of days since TC-510 infusion will be reported in

the category of death less than or equal to 30 days since TC-510 infusion, and death greater than 30 days since TC-510 infusion. A by-subject listing of death will be provided.

10.11.3 Clinical Laboratory Data

The list of all clinical laboratory tests is provided in Appendix B of the protocol. Local laboratories will be used for laboratory safety evaluations in this study. Laboratory normal ranges will be provided by the local laboratory. Hematology and chemistry laboratory parameters, as well as C reactive protein (CRP), will be reported in this analysis. Only hematology/chemistry parameters where an NCI CTCAE v5.0 scale exists will be reported as part of this SAP, and results will be graded according to the NCI CTCAE v5.0 severity grade. Grades can only be assigned where the units are present, and where the normal range is present for parameters whose grades require the lower limit of normal (LLN) or upper limit of normal (ULN). CRP grading will be adopted from a published source[4] (details provided below).

All laboratory values will be reported in SI units unless an alternative convention is more commonly used. For all laboratory analyses described below, only assessments that occurred between lymphodepletion chemotherapy and end of interventional phase will be considered.

Shifts in grade from baseline to the worst grade post-treatment will be summarized for hematology and chemistry parameters across visits. Shift tables will categorize each subject according to their grade at baseline (as defined in section 6.1.1) and the worst grade post-treatment. All percentages will be provided with respect to the number of subjects in the mITT population.

Listings of all individual values meeting CTCAE grade ≥3 will be provided for hematology and chemistry parameters. This will include the subject identifier, tumor type, laboratory test, result, unit, visit, study day, and grade.

Any laboratory values reported as a character value, such as <40, will be transformed into numerical values for use in summaries given by following the specified rules. If a laboratory value is reported using the less than symbol, '<', 0.001 will be subtracted from the original numeric value (as already applied to the study database). If a laboratory value is reported using the greater than symbol, '>', 0.001 will be added to the original numeric value. The same guidelines apply to analyses of cytokines and persistence.

Shift from baseline will also be summarized for CRP using the same conventions as described above, however instead of grades, elevation categories will be used to represent severity which has been obtained from a published source[4]. These categories are described in Table 3 below, along with the range of values required to meet each category. The summary table will display categories as described in Table 3 below.

Table 3. CRP Elevation Categories and Ranges

CRP Elevation Category	CRP Values (mg/dL)
Normal	<0.3
Normal or Minor Elevation	0.3 - <1.0
Moderate Elevation	1.0 - <10.0
Marked Elevation	10.0 - <50.0
Severe Elevation	≥50.0

An additional summary will be produced summarizing high CRP or abnormal hematology. This will include reporting the number and percentage of subjects meeting maximum grade 3 or maximum grade 4 separately for WBC (white blood cells), NEUT (neutrophils), LYM (lymphocytes), and PLAT (platelets) hematology parameters. The same will be provided for CRP, with the "Marked Elevation" category assigned as grade 3, and "Severe Elevation" category assigned as grade 4 for the purposes of this summary.

Subjects must have a grade 3 event to be included in the maximum grade 3 category. If the subject has a grade 4 event, they will be included in the maximum grade 4 category only.

10.11.4 Replication Competent Lentivirus (RCL)

No programmatical outputs will be produced on RCL, but results will be discussed within the aCSR.

10.11.5 TC-510 Persistence

Persistence data (number of vector copies per microgram of DNA) over time will be displayed by line plots.

10.11.6 Cytokines

Cytokine data will be summarized using summary statistics at baseline and for every subsequent scheduled visit post-baseline. Only the following parameters will be included in this summary: IFNg, IL-6 and TNF-a.

10.11.7 Prior and Concomitant Medications

All medications will be collected from the time the subject signs the informed consent form and throughout the subject's participation in the interventional phase. Prior and concomitant medications will be coded using the WHO Drug B3 Global, March 2021.

Medications will be assigned to a time period (prior and/or concomitant) as follows:

- If both the start and stop date exist and are before the first lymphodepleting therapy date, the medication will be counted as prior.

- If the start date is on or after the first lymphodepleting therapy date, the medication will be counted as concomitant.
- If the start date is before the first lymphodepleting therapy date and the stop date is after the first lymphodepleting chemotherapy or the medication is continuing, the medication will be counted as prior and concomitant.
- If the start date is missing and the stop date is before the first lymphodepleting chemotherapy, the medication will be counted as prior.
- If the start date is missing and the stop date is after the first lymphodepleting therapy date or the medication is continuing, the medication will be counted as concomitant.
- If the start and stop dates are missing and the subject gets lymphodepletion the medication will be counted as concomitant.

A by-subject listing of all prior and concomitant medication data will be provided for the mITT population, including: subject identifier, age, sex, race, tumor type, start date, end date, duration (days), Anatomical Therapeutic Chemical 3rd level (ATC-3) class, preferred term, indication type and indication, dose, frequency, route, and status (prior [P], concomitant [C], prior and concomitant [PC]). Duration (days) will not be provided if either the start or stop/end date is partial or missing.

10.11.8 Blood Transfusions

A by-subject listing of blood transfusions will be provided for the mITT population.

11 Changes to Protocol Specified Analysis

A list of all changes to protocol specified analyses is provided below. The majority of changes are due to the study terminating early, thus only an abbreviated CSR and simplified set of analyses being required.

- Throughout the protocol, the day of TC-510 infusion is stated as Day 0, however for all analyses as part of this SAP, TC-510 infusion is re-defined as Day 1 (Day 1 consistently used across ADAP studies). All subsequent study days post-TC-510 infusion is therefore one greater than it would be under the protocol definition.
- Data will not be presented by dose group as stated throughout section 14 of the protocol, as all dosed subjects received the initial dose DL0 in phase 1.
- In the first paragraph of section 14, the protocol states “All efficacy and safety data will be summarized by cohort and across cohorts”. This data will not be presented by cohort as Phase 2 of the study was never initiated.
- ITT population definition included in this SAP refers to the pre-screening informed consent form to be specific and avoid misinterpretation.
- mITT population definition included in this SAP has been changed to remove the requirement for receiving the ‘planned dose’ and allow for any dose.
- In addition to 80% 2-sided confidence intervals being produced in efficacy analyses, 95% 2-sided confidence intervals will also be provided.
- Protocol section 14.2: The trial success criterion of 1 response in each Phase 2 disease cohort was not applied as the Phase 2 portion of the study was never initiated.
- Protocol section 14.3.1 states that all CRF data will be listed, however only a subset of the full data will be provided in data listings based on the abbreviated reporting requirements of the study.
- Protocol section 14.3.2: The set of disposition categories described in the protocol is different to what will be included in disposition outputs. The list of demographic information in the protocol stated to be summarized is different to that described in this SAP. The protocol states that medical history will be

summarized using descriptive statistics, but medical history will not be summarized as part of this SAP; only a listing will be provided.

- Protocol Section 14.3.3: Duration of the infusion, saline flush volume, and exposure to lymphodepleting chemotherapy will not be included in summary tables as stated in the protocol. Prior and concomitant medications will be listed only, and not tabulated by counts and percentages as stated in the protocol.
- DLTs will not be presented in a summary table as stated in protocol section 14.3.4.1 as this was not available in the eCRFs, but will be described separately in the aCSR.
- Protocol section 14.3.4.1 states that the overall safety profile of the study drug will be evaluated in the safety set. The mITT population has been redefined in this SAP to align more closely with the safety set definition, and therefore the mITT population will be used primarily to summarize the safety profile of TC-510.
- In section 14.3.4.1 of the protocol, not all the clinical laboratory analyses, and no analyses of vital signs, will be conducted as part of this SAP. Further, clinical laboratory analyses will not be summarized by visit.
- System organ class, and premature discontinuation from the study drug and from the study participation due to adverse events, will not be presented in safety summaries as stated in section 14.3.4.1 of the protocol.
- Section 14.3.4.1 of the protocol states that mortality rates will be summarized up to day 15 and day 25, but rates will be displayed for deaths ≤30 days and >30 days from infusion TC-510.
- DoR, TTR, PFS and OS will not be reported in this SAP as stated in protocol section 14.3.4.2. As no time-to-event endpoints are being evaluated, no Kaplan-Meier methods described in the protocol will be conducted.
- Section 14.2 and 14.3.4.2 of the protocol states that DCR is defined as the ORR plus the proportion of patients with SD lasting at least 12 weeks. Elsewhere in the protocol (e.g. Study Objectives), the threshold for SD is 8 weeks. A threshold of 8 weeks will be used for the analysis of DCR.

- None of the analyses described in section 14.3.5 of the protocol pertaining to Phase 2 will be conducted, as this phase of the study was never initiated.

12 References

1. Eisenhauer EA, et al. New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1) 2009; Eur J Ca 45:228-247.
2. EMEA/CHMP/GTWP/60436/2007 Guideline on follow-up of patients administered with gene therapy medicinal products, October 2009.
3. FDA (2006a). Guidance for Industry, Gene Therapy Clinical Trials-Observing Subjects for Delayed Adverse Events (November 2006). Updated from the 2000 FDA Guidance.
4. Nehring SM, Goyal A, Patel BC. C Reactive Protein. [Updated 2023 Jul 10]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK441843/