Study Title: Phase 1 Dose Escalation, Multi-tumor Study to Assess the Safety, Tolerability and Antitumor Activity of Genetically Engineered MAGE-A4c1032T in HLA-A2+ Subjects with MAGE-A4 Positive Tumors

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Adaptimmune LLC

ADP-0044-001

Phase 1 dose escalation, multi-tumor study to assess the safety, tolerability and antitumor activity of genetically engineered MAGE-A4c1032T in HLA-A2+ subjects with MAGE A4 positive tumors.

Statistical Analysis Plan

Version: 3.1

[redacted]

SPONSOR SIGNATURE PAGE

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Approved by: _____ 19 November 2020_____
[redacted] Date
Biostatistician, Biometric
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Signatures below confirm that the Statistical Analysis Plan was developed in accordance with [redacted] and that it is approved for release.

This document has been approved and signed electronically on the final page by the following:

	Signatory
Author	[redacted] Project Role: Biostatistics Lead

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REVISION HISTORY

Version No.	Effective Date	Summary of Change(s)
Final 1.0	02NOV18	New document
Final 2.0	01JUN2020	New Template. Updates include Second infusion and radiation, definition of TEAE, and censoring rules.
Final 3.0	12NOV2020	Comments received on 9-NOV-2020 resolved
Final 3.1	19NOV2020	Comments received on 18-NOV-2020 resolved

LIST OF ABBREVIATIONS

Abbreviation / Acronym	Definition / Expansion
ADaM	Analysis Data Model
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine Aminotransferase
ATC - 3	Anatomical Therapeutic Chemical Class 3
AST	Aspirate Aminotransferase
BMI	Body Mass Index
BOR	Best Overall Response
BP	Blood pressure
Bpm	Beats per minute
CARTOX	CAR T Cell Therapy Toxicity Test
CI	Confidence Interval
CR	Complete Response
CRS	Cytokine Release Syndrome
CSR	Case Study Report
DBP	Diastolic blood pressure
DNA	Deoxyribonucleic acid
DoSD	Duration of Stable Disease
DoR	Duration of Response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
INR	International Normalized Ratio
ITT	Intent-to-Treat
mITT	Modified Intent-to-Treat
MTD	Maximum tolerated dose
MedDRA	Medical Dictionary for Regulatory Activities
ORR	Overall Response Rate
OS	Overall Survival

Abbreviation / Acronym	Definition / Expansion
PD	Progressive Disease
PFS	Progression Free Survival
PR	Partial Response
PT	Preferred Term
QT	The QT interval is measured from the beginning of the QRS complex to the end of the T wave
QTc	corrected QT interval
QTcB	QT corrected using Bazzett's formula
QTcF	QT corrected using Fridericia's formula
RCL	Replication Competent Lentivirus
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SD	Stable Disease
SOC	System Organ Class
TEAE	Treatment-emergent adverse event
TTR	Time to Response
TCR	T Cell Receptor
WHO-DD	World Health Organisation - Drug Dictionary

1 INTRODUCTION

This document provides a description of statistical methods and procedures to be implemented for the analysis of data in relation to efficacy and safety analyses for Study ADP-0044-001, based on the study protocol version amendment 07 (June 4, 2019) and the electronic Case Report Form (eCRF) dated (November 1, 2019).

Any deviation from the final version of this Statistical Analysis plan (SAP) will be supported by sound statistical rationale and will be documented in the final Clinical Study Report (CSR).

1.1 Study Overview

ADP-0044-001 is a Phase I dose-escalation and expansion adoptive T cell therapy study, seeking to suppress the MAGE-A4 protein in multiple tumor types. The study is conducted using a modified 3+3 design assessing safety, tolerability, and anti-tumor activity. Once a maximum tolerated dose (MTD) is identified an additional 30 subjects may be enrolled and treated at the MTD.

After a subject is screened and meets all inclusion exclusion criteria, the subject will undergo Leukapheresis. Leukapheresis is a procedure conducted to obtain starting material to manufacture the autologous MAGE-A4^{c1032} T cells. Once the T cell product has been manufactured, the subject will proceed to have lymphodepleting chemotherapy (days -7 to -4) and followed by MAGE-A4^{c1032} T cell infusion (day 1).

Subjects may be eligible to receive a second T cell infusion a minimum of 6 weeks after the first infusion.

Up to an additional 10 subjects will be treated in a radiation sub-study (ADP-0044-001R) and will receive the MTD MAGE-A4^{c1032} T cells after lymphodepleting chemotherapy in combination with low dose radiation. These subjects will not be reported in the CSR and will be reported separately.

Subjects will remain in the interventional phase of the study until disease progression, death, or withdraw of consent. All subjects on study are followed in long term follow-up for safety and anti-tumor activity 15 years after their last T cell infusion.

2 STUDY OBJECTIVES

2.1 Primary Objective(s)

To evaluate safety and tolerability of autologous genetically modified T-cells (MAGE-A4^{c1032}T) in subjects with HLA-A*02 and MAGE-A4 positive inoperable locally advanced or metastatic tumors.

2.2 Secondary Objective(s)

- To evaluate the anti-tumor activity of initial infusion of autologous genetically modified T-cells (MAGE-A4^{c1032}T) in HLA-A*02 subjects with MAGE-A4 positive inoperable locally advanced or metastatic tumors;
- To evaluate potential gene therapy-related delayed adverse events for 15 years post infusion;

2.3 Exploratory Objective(s)

- To evaluate persistence, phenotype and functionality of transduced (MAGE-A4^{c1032}T) and non-transduced T-cells
- [redacted]
- To evaluate the anti-tumor activity in subjects that receive a second infusion of autologous genetically modified T-cells (MAGE-A4^{c1032}T)
- To evaluate the anti-tumor activity in subjects that receive their first anticancer treatment regimen (systemic therapy, radiation therapy, or surgery) after progression on autologous genetically modified T cells (MAGE-A4^{c1032}T) with (ADP-0044-001R substudy) or without (main study) Low Dose Radiation.

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

There are 3 planned cell dose groups, with the initial dose group being 0.1×10^9 transduced cells, then 1×10^9 and 5×10^9., and then the expansion group. See Table 1 for the total number of subjects able to be enrolled in each cell dose group.

Figure 1 displays the study schematic and relative study days for ADP-0044-001. For details specific to each procedure or treatment period, such a leukapheresis, lymphodepletion chemotherapy, and T cell infusion, please refer to the protocol section 3.2.

There are 3 phases in the overall study design: Screening Protocol, Screening and Interventional Phase, and Long-Term Follow-up Phase.

Screening Protocol (ADP-0000-001)– Once subjects have been screened for the presence of HLA-A*02 and MAGE A4 expression on the tumor based on the screening protocol, and confirmation of presence is given, the subject signs the informed consent. Upon signing informed consent, the subject enters the screening phase and is assessed for the inclusion/exclusion criteria. If all eligibility criteria are met, the subject moves into the interventional Phase.

Screening and Interventional Phase (ADP-0044-001) – There are up to two parts to the interventional phase. The interventional phase runs from confirmed subject eligibility up to death, withdrawal, or disease progression. Subjects may receive a second infusion during the interventional phase. Re-assessment of baseline values will be calculated as mentioned in Section 4. The start of the interventional phase is not considered Study Day 1.

Long Term Follow-Up Phase (ADP-0044-001) – The long-term follow-up (LTFU) phase starts once a subject ends the interventional phase and runs up to 15 years after the last T cell infusion to continue long term monitoring for potential gene-therapy related adverse events or until death or withdrawal of consent.

Table 1: Cell Dose Groups

Group	Number of Subjects	Transduced cells[1]	Interval for Safety Review
1	3 to 6	0.1×10^9 (±20%) transduced cells	21-day observation period
2	3 to 6	1×10^9 (range: 0.5 to 1.2×10^9) transduced cells	7-day observation period[2]
3[4]	3 to 6	5×10^9 (range: 1.2 to 6×10^9) transduced cells	7-day observation period[2]
Expansion[4]	Up to 30	5×10^9 (range: $1.2 \times 10^9 - 10 \times 10^9$)[3]	

[1] For subjects in all cell dose groups whose cells fail to meet the cell dose requirement during the manufacturing process, re-leukapheresis and/or re-manufacturing may be requested.
[2] If in any Group, 1 out of 3 subjects experiences a DLT requiring expansion of an additional 3 subjects (n=6), the observation period will be increased from 7 days to 14 days for the 3 subsequent treated subjects
[3] If Group 3 is selected as the optimal dose group and expanded to 30 subjects, the maximum dose range will be increased to 10×10^9 transduced cells for the subjects in the expansion cohort (ie. after 3-6 subjects are treated in the dose escalation stage) and for subjects in the substudy population.

[4] Group 3 will be treated with Cyclophosphamide 600mg/m2/day on Days -7, -6, -5 and fludarabine 30 mg/m2/day on Days -7, -6, -5 and -4 as described in Table 4.

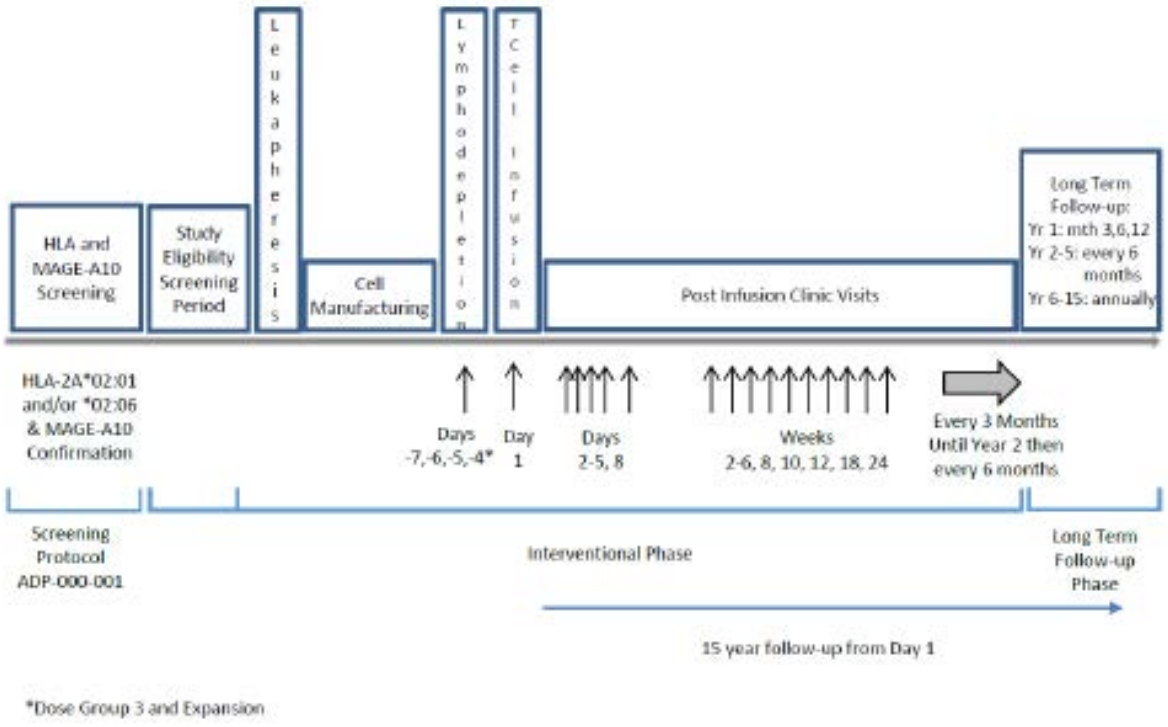

Figure 1: Overall Study Design

3.2 Analysis Sets

The **intent-to-treat** (ITT) population includes all subjects who are enrolled in the study.

The **modified ITT** (mITT) population includes all subjects in the ITT population who receive at least one MAGE-A4^{c1032}T-cell infusion.

The demography summaries will be based on the ITT population, unless otherwise stated.

The safety and efficacy summaries and analyses will be based on the mITT population, unless otherwise stated.

A by-subject listing of analysis population details will be provided. This listing will be presented by treatment group and will include subject identifier, inclusion/exclusion flag for each population, and reason for exclusion from each population.

4 STATISTICAL METHODS

4.1 Sample Size Justification

The sample size is based on clinical judgment. The study is not powered for either safety or efficacy and hence the data will be summarized descriptively. No formal hypothesis testing is planned.

Up to 30 subjects total at the selected dose group (inclusive of subjects accrued during the dose escalation) will be treated across all the eligible tumor types in the dose expansion phase. Up to 10 additional subjects will be treated in the sub-study.

The DLTs in maximum sample size of 30 subjects in the expansion phase plus up to 10 subjects in the sub-study (total maximum number of subjects = 40) will be assessed using Bayesian methods. DLT analysis will be performed by Adaptimmune and will not be included in CSR Table, Listing and Figure.

4.2 Data Quality Assurance

All tables, figures and data listings to be included in the report will be independently checked for consistency, integrity [redacted]

4.3 Examination of Subgroups

Important demographic, efficacy and safety summaries will be examined for the tumor type subgroup of synovial sarcoma. All the Synovial Sarcoma subjects had T-Cell infusion and in Group 3 and Expansion, hence the summaries will be based on mITT population in Group 3 plus Expansion.

No formal statistical analysis will be performed within subgroup.

4.4 General Presentation Considerations

Unless specified otherwise, 'Baseline' for first infusion is defined as the last available non-missing assessment prior to lymphodepleting chemotherapy. Baseline for second infusion is defined as the last available assessment 7 days before second lymphodepleting chemotherapy regimen.

'Study Day' will be calculated relative to the date of T cell infusion. i.e. Study Day = Assessment Date -T Cell Infusion Date + 1.

Durations are calculated as the stop date minus the start date plus one.

For elapsed time (e.g. time since the initial diagnosis) if the reference date is on or after the event date, then the elapsed time is the reference date minus the event date plus one. If the reference date is before the event date, then the elapsed time is the reference date minus the event date.

Unscheduled assessments (laboratory data, scans, ECG, vital signs, etc. 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 more than one laboratory value is available for a given visit, the first valid observation will be used in summaries and all observations will be presented in listings. If it is not possible to determine which is the first measurement due to missing times, then the average of all measurements for that time point will be used as the value for that time point.

Continuous data will be summarized in terms of the mean, standard deviation, median, minimum, maximum and number of observations, unless otherwise stated.

Continuous data that are expected to be skewed will be presented in terms of the maximum, upper quartile, median, lower quartile, minimum 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.

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

Percentages will be presented to two decimal places. Percentages will not be presented for zero counts. Percentages will be calculated using n as the denominator. If sample sizes are small, the data displays will show the percentages, but any textual report will describe frequencies only.

Changes from baseline in categorical data will be summarized using shift tables where appropriate.

P-values greater than or equal to 0.001, in general, will be presented to three decimal places. P-values less than 0.001 will be presented as "<0.001".

Confidence intervals 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.

4.5 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. In addition, imputed dates are not used for deriving the last contact date in the overall survival analysis dataset.

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

The partial date imputation will follow ADaM conventions. The ADaM approach is to populate the numeric date variables with the imputed date and add a flag variable to the dataset that indicates the level of imputation.

The flag variable can contain the values: blank, 'D', 'M', 'Y'.

blank: indicates that no imputation was done

- D='Day': indicates that the day portion of the date is imputed
- M='Month': indicates that the month and day portions of the date are imputed
- Y='Year': indicates that the entire date (year, month, and day) is imputed

Imputing partial AE, medical history and prior/concomitant medication start dates:

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, month and day are unknown, then:

1. If the year matches the first dose date of lymphodepleting chemotherapy:
   - If the imputed stop date is available and complete and is on or after the first lymphodepleting chemotherapy date and before the second Lymphodepletion chemotherapy date, then impute to the month and day of the first lymphodepleting chemotherapy date.
   - If the imputed stop date is available and complete and is on or after the second lymphodepleting chemotherapy date, then impute to the month and day of the second lymphodepleting chemotherapy date.
   - If the imputed stop date is missing or no stop date is applicable, then impute to the month and day of the first lymphodepleting chemotherapy date.

2. If the year matches the first dose date of lymphodepleting chemotherapy for the first infusion and the imputed stop date is available and complete and not on or after the first lymphodepleting chemotherapy date, then impute to the first day of the month of the imputed stop date.

3. Otherwise, assign first day of January.

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. If the month and year match the second lymphodepleting chemotherapy date, then impute to the day of the second lymphodepleting chemotherapy date.
3. Otherwise, assign '01' of the month.

Imputing partial AE, medical history 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'.

c) If the day is unknown, then impute to the last day of the month.

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 post-lymphodepletion period.

4.6 Software

All report outputs will be produced using SAS® version 9.4 [4] or a later version in a secure and validated environment.

All report outputs will be provided to the Sponsor in either Microsoft Word .rtf format or .pdf format according to FDA Portable Document Format (PDF) Specifications.

4.7 Study Subjects

4.7.1 Disposition of Subjects

A clear accounting of the disposition of all subjects who enter the study will be provided, from screening to study completion. Summaries of subject disposition presented by dose group and overall will be provided as follows:

- Number of subjects in the analysis populations
- Number of subjects who completed leukapheresis and/or lymphodepleting chemotherapy.
- Number of subjects who received a second infusion.
- Number of subjects who are on going in Interventional Phase.
- Number of subjects who completed/discontinued the Interventional Phase (including the reasons for discontinuation)
- Number of subjects in LTFU phase.
- Number and percentage completed the study

By-subject listings of infusion dates, and withdrawal details (including reason for discontinuation and days on study) will also be provided.

4.8 Demographics and Baseline Characteristics

The following demographic and baseline characteristics will be summarized and listed for subjects in the ITT population and mITT population by treatment group:

- Age at time of informed consent (in years, as a continuous variable)

- Age categorization (<65, >= 65 years)
- Sex (Male, Female)
- Race (White, Black/African American, Asian, American Indian/Alaska Native, Hawaiian Native/Other Pacific Islander, Unknown, Other, Decline to State)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Unknown, Decline to State)
- Weight at baseline (in kilograms)
- Height at baseline (in centimeters)
- BMI at baseline (in kg/m^2) calculated using weight and height at baseline Primary Tumor Type (Esophageal, Gastric, Head/Neck, Melanoma, Non-Small Cell Lung Cancer, Ovarian, Urothelial, Myxoid/Round Cell Liposarcoma, Synovial Sarcoma)
- Time since initial diagnosis
- Time from initial diagnosis to T cell infusion
- Prior Lines of Systemic Therapy (as a continuous variable)
- Prior Lines of Systemic Therapy categorization (0, 1, 2, 3, 4+)
- Bridging therapy categorization (Yes, No)
- Baseline Eastern Cooperative Oncology Group (ECOG) performance

Since age is part of the inclusion criteria, age will be reported as the number of complete years at the date of informed consent.

4.9 Medical History

Medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 23.0.

The number and percentage of subjects with each medical history condition collected on the eCRF will be summarized for the ITT population and mITT population for each cell dose group and overall.

A by-subject listing of all medical history terms will also be created.

4.10 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 World Health Organization Drug Dictionary (WHO-DD) version (Mar 2019).

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 lymphodepleting chemotherapy, the medication will be counted as prior.
- If the start date is on or after lymphodepleting chemotherapy, the medication will be counted as concomitant.

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

Summaries showing number of subjects and percentage taking each medication categorized by the WHO-DD Anatomical Therapeutic Chemical 3rd level (ATC-3) will be provided for each medication preferred term by dose group and overall in the mITT population. This will be done separately for prior and for concomitant medications.

A by-subject listing of all prior and concomitant medication data will also be provided.

4.11 Treatment Exposure

T-cell dose is based on the total number of transduced cells reported on the T-cell infusion eCRF page in units 10^6. Cell dose will be reported as stated in the protocol in units of 10^9. The total number of transduced cells (in billions) will be summarized for first infusion in the mITT population by cell dose group and overall using descriptive statistics.

A by-subject listing of first infusion and second infusion will also be provided

All lymphodepleting chemotherapy dose administration data including Cyclophosphamide, Fludarabine, and Mensa will be presented by subject in a data listing.

4.12 Efficacy Evaluation

Tumor response will be assessed using RECIST v1.1 criteria [1]. Subjects will undergo assessments at baseline, Week 6, 12, 18, 24, and every 3 months for two years and every 6 months post-infusion or until radiological disease progression is documented.

All subjects will be followed until death from any cause (unless the subject is lost to follow-up, withdraws consent for the entire study, or the sponsor terminates the study early).

4.12.1 Analysis and Data Conventions

No formal testing of hypotheses has been planned in this study.

By subject listing will be based on ITT population. All the data from each visit will be presented in the listings, including the first and second infusion.

Summary tables of AEs will include first infusion only.

Tables of efficacy analysis will include first infusion only, except the following scenarios:

- Overall Survival analysis, in which case data in second infusion and LTFU will be considered.
- Progression Free Survival analysis, if a subject discontinued the interventional phase without any documented PD, but then died during LTFU, then the subject will be considered as progressed at the date of death.

Tables of lab values will include first infusion data only. Separate table for Synovial Sarcoma Subgroup will be provided.

Summary table of lab parameters will be based on scheduled visits only. Shift tables and listings will be based on all the visit, including the unscheduled visits.

Table of Prolonged Cytopenia will include all the visits for the first infusion only, including the unscheduled visits and will be summarized based the reporting windows specified in section 4.13.2. By subject listing of Prolonged Cytopenia will report all the visits, including the second infusion.

Efficacy analyses will be summarized with summary statistics for mITT population.

For subjects receiving a second infusion, baseline is re-established prior to the second infusion and the subject will be censored in first infusion efficacy analyses following the censoring rules described in Section 4.12.2

4.12.1.1 Multi-center Studies

All centers will be pooled together in the efficacy analyses. If the results reveal impact of the centers, then ad hoc analyses will be performed.

4.12.1.2 Multiple Comparisons/Multiplicity

No formal statistical testing or interim analyses are planned. Hence no adjustments for multiplicity are required.

4.12.1.3 Examination of Subgroups

Subgroup analyses will be conducted for Sarcoma subjects (mITT) for selected tables, listings and figures.

4.12.2 Efficacy Variables

Best Overall Response (BOR)

Best overall response (BOR) is determined once all assessments from baseline until disease progression, death, or discontinuation of interventional phase for infusion one, whichever occurs first, are recorded. It is defined as the best response across all assessments where per protocol confirmation of complete response (CR) and partial response (PR) are necessary for BOR

determination. 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. Unconfirmed CR or PR will not be considered as BOR. In case of SD, it must have occurred at least 39 days(visit window of 42 days ± 3 days) from baseline; otherwise, BOR will depend on subsequent assessments. BOR will be presented as PD, regardless of duration.

To take into account potential pseudoprogression, no tumor assessments prior to the 39 day window from baseline will be considered for BOR determination, unless there is unequivocal progression of existing non-target lesions and/or the appearance of new malignant lesions. Please refer to the Section 7.4.8 of the protocol for additional information.

If a subject receives any subsequent anti-cancer therapy(anti-cancer surgery/procedure, anti-cancer radiotherapy, curative anticancer therapies and anti-cancer surgeries other than the study treatment, not including approved palliative radiation and diagnostic procedures such as surgical biopsies) (see protocol section 6.2 for more information), during the interventional phase, in general, BOR will be determined using all tumor response assessments up to the start date of the first subsequent anti-cancer therapy.

For subjects that receive second infusion, BOR for first infusion will be determined using all tumor responses up to last assessment prior to the baseline assessment for the second infusion. Baseline is re-established prior to second infusion with a tumor assessment within 7 days prior to lymphodepleting chemotherapy for the second infusion.

The overall visit response will be derived programmatically in accordance with RECIST v 1.1 criteria [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.

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 prior to 39 day window will be presented.
- If a subject only has tumor assessments prior to 39 day window as of data cut date, then BOR=NE

The programmatically derived overall visit response will be used for all efficacy endpoints, where applicable.

The BOR for first infusion for each subject will be summarized (number and percentage of subjects in each category).

A by-subject listing will be provided reporting both the derived response and the investigator's response.

Overall Response Rate (ORR)

ORR is defined as the proportion of subjects with best overall response (BOR) of confirmed CR or confirmed PR, according to the RECIST 1.1 among subjects with measurable disease at baseline. Subjects with unknown or missing response will be treated as non-responders (i.e., they will be included in the denominator when calculating the proportion).

The number and proportion of subjects achieving confirmed response will be summarized and presented by dose group and overall for the mITT population. The associated 95% Wilson and exact confidence intervals (CI) will be calculated. In the expansion cell dose group only, the Bayesian 95% credible interval and posterior mean will also be reported.

If p represents the response rate for the T cell receptors (TCR), assuming the number of subjects with response = Yes, x, in n subjects follows a binomial distribution, B(n, p), and a non-informative prior distribution, such as a beta(0.1, 0.9) for p, the posterior follows a beta(0.1 + x, 0.9 + n - x) distribution. This posterior will be used to compute the mean and 95% credible interval.

Maximal change in target lesions from baseline will be shown in a waterfall plot by each cell dose group and overall. Change in target lesions from baseline over time by patient will be shown in a spider plot.

Time to Response (TTR)

Time to response (CR or PR) is defined as the interval between the date of first T-cell infusion and the earliest date of first documented confirmed CR or confirmed PR.

- TTR (in weeks)= [date of initial confirmed CR or PR – date of T-cell infusion+1]/7

TTR will be summarized and displayed graphically in weeks using the Kaplan-Meier methodology to estimate the 25th, 50th (median), 75th percentiles, Min and Max.

Median event times and corresponding two-sided 95% CIs for the medians will be provided for TTR.

Progression Free Survival (PFS)

PFS is defined as the time from first T cell infusion date to the first date of radiological progressive disease (PD) or death date (due to any reason), whichever event is earlier. PFS in weeks will be calculated as: (first event date – first T cell infusion date + 1) / 7. The details regarding the handling of missing assessment and censoring for primary PFS analysis are presented as follows:

- If there are no post baseline tumor assessments after T cell infusion or date of death recorded, PFS will be censored and have a duration set to 1.
- If a subject is known to be alive and progression-free, PFS will be censored on the day of the last tumor assessment.
- If a subject is given anti-tumor treatment (anti-cancer surgery/procedure, anti-cancer radiotherapy, curative anticancer therapies and anti-cancer surgeries other than the study treatment, not including approved palliative radiation and diagnostic procedures such as

surgical biopsies) prior to PD or death, PFS will be censored on the date of the last tumor assessment prior to the start date of the anti-tumor treatment.

- If a subject receives a second T cell infusion prior to PD or death, PFS will be censored on the date of the last tumor assessment prior to the baseline for the second infusion.
- If a subject discontinues the interventional phase prior to PD, PFS will be censored on the date of the last tumor assessment.
- If a subject misses 2 or more consecutive post-baseline tumor assessments and the following assessment is a PD, PFS will be censored on the date of the last tumor assessment

PFS will be summarized based on mITT population using the Kaplan-Meier method. These summaries will include 6, 12, 18, and 24-weeks survival probabilities along with corresponding 95% CIs by dose cohort, Group 3 + Expansion, and overall. In the expansion cell dose group, PFS will be summarized and displayed graphically using Kaplan-Meier (K-M) methodology to estimate the 25th, 50th (median), 75th percentiles. Median event times and corresponding two-sided 95% CIs for the medians will be provided for PFS.

When determining PFS, the recorded date of progression (defined as first time at which progression can be declared) will be used. For progression due to the presence of a new lesion, the date of progression is the first date that the new lesion was observed. If multiple assessments based on the sum of target lesion measurements are done at different times, the date of progression is the date of the first observation or radiological assessment of target lesions that shows a predefined increase in the sum of the target lesion measurements.

A by-subject listing of the PFS data will be provided.

Sensitivity Analyses on PFS

Sensitivity Analysis #1 will consider the initiation of new anti-tumor treatment to be an event. PFS will be progressed at the date of starting alternate anti-cancer treatment

Sensitivity Analysis #2 will be conducted to assess the impact of missed or not evaluable (NE) tumor assessments. This analysis will backdate any PD events that occur immediately after missing or NE assessments. If the PD occurs immediately after NE assessment (or series of NE assessments), the PD date will be the date of the first NE assessment preceding the PD. If the PD occurs immediately after a missed assessment (or series of missed assessments), the PD date will be the date of the first missed assessment preceding the PD. Death or documented progression after missed visits will be considered as censored at the date of last adequate assessment prior to missing visits.

Sensitivity Analysis #3 will consider discontinuation from the interventional phase for clinical progression will be considered as progressed at date of discontinuation from the interventional phase.

Note: Similar to the primary analysis, the subjects who discontinue from the intervention period due to adverse event, should be censored at the last tumor assessment prior to the end of interventional phase for this sensitivity analysis.

All sensitivity analyses will use the same statistical methods as the main PFS analysis.

Overall Survival (OS)

OS is defined as the time from the date of first T cell infusion to the date of death (due to any reason). OS in weeks will be calculated as: (death date – first T cell infusion date + 1) /7. Censoring will occur as follows:

- If there is no confirmation of death, OS will be censored on the date the subject is last known to be alive, or the data cutoff date, or the end of study date, whichever is earlier.

OS will be summarized for the mITT population using the Kaplan-Meier method. These summaries will include 6, 12, 18, and 24-weeks survival probabilities along with corresponding 95% CIs. In the expansion cell dose group, OS will be summarized and displayed graphically using Kaplan-Meier (K-M) methodology to estimate the 25th, 50th (median), 75th percentiles Median event times and corresponding two-sided 95% CIs for the medians will be provided for OS.

Duration of Response (DoR)

DoR is measured from the time criteria are first met for CR/PR (whichever is first recorded) until the first date of progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded on study). This will only apply to subjects with confirmed CR or confirmed PR and will be calculated as: (first event date – first OR date + 1)/7. Censoring will occur as follows:

- If a subject is known to be alive and progression-free, DoR will be censored on the date of the last tumor assessment.
- If a subject dies of any cause in the absence of documented PD, DoR will be censored on the date of the last tumor assessment.
- If a subject is given subsequent anti-tumor treatment (anti-cancer surgery/procedure, anti-cancer radiotherapy, curative anticancer therapies and anti-cancer surgeries other than the study treatment, not including approved palliative radiation and diagnostic procedures such as surgical biopsies) prior to PD or death, DoR will be censored on the date of the last progression-free tumor assessment prior to the start date of the anti-tumor treatment.
- If a subject is given a second infusion prior to PD or death, DoR will be censored on the date of the last tumor assessment prior to re-establishing baseline for the second infusion.
- If a subject ends the interventional phase of the study prior to PD, DoR will be censored on the date of last progression-free tumor assessment.

Summaries and graphical displays for DoR using Kaplan-Meier method will be the same as those for OS. This analysis, however, will only apply to subjects that have achieved confirmed CR/PR.

A swimmer plot will be created indicating subject's BOR, duration of response, PD, second T cell infusion and death.

Sensitivity Analyses on DoR

Sensitivity Analysis #1 will also consider death to be an event. If death occurs before PD is documented, the date of death will be used for the DoR event calculation.

Duration of Stable Disease (DoSD)

DoSD is defined as the time from the date of T Cell infusion to first date of radiological PD. This will only apply to subjects with BOR as confirmed CR, confirmed PR, or confirmed SD and will be calculated as: (first event date –date of T Cell Infusion+ 1)/7.

Censoring rules and summaries for DoSD will be the same as those for DoR.

4.13 Safety Evaluation

All safety summaries and analyses will be based upon the mITT population as defined in Section 3.2 of this SAP.

4.13.1 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 23.0. Adverse events will be graded according to the NCI CTCAE v 5.0.

A treatment-emergent adverse event (TEAE) in the interventional phase is defined as an AE (identified by PT) that begins or is on-going on or after the first day of lymphodepleting chemotherapy has been administered until discontinuation from the interventional phase . Treatment-related TEAEs are those with reasonable causality to Lymphodepletion or T-Cell marked as "definitely related", "probably related", or "possibly related" on the eCRF. TEAEs with an outcome of death are those with a grade of 5 or an outcome of "fatal."

Second Infusion TEAE are defined as an AE that starts or increases in severity/toxicity after the first day of the second lymphodepleting chemotherapy has been administered until discontinuation from interventional phase . If an AE or TEAE from the first infusion is ongoing at the time of second infusion, it will not be summarized as an TEAE in the second infusion unless it increases in toxicity grading after lymphodepleting chemotherapy begins.

An AE in the long-term follow-up (LTFU) period is defined as an AE that starts or increases in severity/toxicity after discontinuation from the interventional period , until discontinuation from the long-term follow-up period. If an AE or AE from the interventional period is ongoing at the start of the long-term follow-up period, it will not be summarized as an AE in the long-term follow-up period unless it increases in toxicity grading after discontinuation from the interventional period.

Summary tables will be presented for AE and TEAEs by dose group. An overall presentation of AE information will include the following:

- Number and percentage of subjects with at least one AE
- Number and percentage of subjects with at least one TEAE
- Number and percentage of subjects with at least one treatment-related TEAE
  - Number and percentage of subjects with a TEAE related to: Cyclophosphamide, Fludarabine, T cell infusion
- Number and percentage of subjects with at least one TEAE of Grade 3 or higher
- Number and percentage of subjects with at least one treatment-related TEAE of Grade 3 or higher
  - Number and percentage of subjects with a TEAE of Grade 3 or higher related to: Cyclophosphamide, Fludarabine, T cell infusion
- Subjects with Drug Interrupted or Drug Reduced AEs
  - Number and percentage of subjects an AE related to: Cyclophosphamide, Fludarabine, T-Cell Therapy
- Number and percentage of subjects with at least one serious TEAE
- Number and percentage of subjects with at least one treatment-related serious TEAE
- Number and percentage of subjects with at least one TEAE with Fatal Outcome

TEAE information will also be presented by NCI CTCAE severity grade and by relationship to study treatment. If a subject had more than one occurrence of a TEAE, the most severe grade will be used in the summary tables.

The following summaries will be provided:

- Number and percentage of subjects for each AE, categorized by PT, all grade and Grades 3 or higher in the ITT population
- Number and percentage of subjects for each TEAE, categorized by PT, and SOC, PT, by all grades and Grades 3 or higher
- Number and percentage of subjects for each TEAE of Grade 3 or higher, categorized by SOC and PT, all grade and Grades 3 or higher
- Number and percentage of subjects for each TEAE, categorized by SOC, PT, and maximum CTCAE grade
- Number and percentage of subjects for each TEAE, categorized by PT and SOC, PT, and relationship to T cell infusion, all grade and Grades 3 or higher
- Number and percentage of subjects for each treatment-related TEAE, categorized by SOC and PT, all grade and Grades 3 or higher
- Number and percentage of subjects for each treatment-related TEAE, categorized by SOC, PT, and maximum CTCAE grade

Summaries will be provided separately for both first infusion and second infusion. A summary of long-term follow-up AEs will also be provided. Please refer to Table 2 for summaries by reporting periods.

Counts will be by subject, not by event, and subjects are only counted once within each SOC or PT. For tables categorized by maximum CTCAE grade, subjects with multiple events within a particular SOC or PT will be counted under the category of their most severe event within that SOC or PT.

A by-subject listing of all AEs (including non-treatment-emergent events) will be provided. This listing will be presented by treatment arm and will include: subject identifier, age, gender, race, adverse event (SOC, PT, and verbatim term), date of onset, date of resolution, duration, CTCAE grade, seriousness, and relatedness. Additionally, by-subject listings for subjects experiencing cytokine release syndrome (CRS), persistence (copies / microgame of DNA) of MAGE-A4^{c1032}T and replication-competent lentivirus (RCL) over time will be provided.

For missing or partially missing dates, imputation will be done according to Section 4.5. 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 first dose study therapy.

Table 2: Summary of AEs by Reporting Period

	AEs (from ICF up to first day of LD)	Interventional Period TEAEs- First Infusion	LTFU Period
AEs by PT	X	X	X
T Cell Related AEs by PT		X	
Serious AEs by PT		X	
T Cell Related Serious AEs by PT		X	
Fatal AEs by PT		X	
AEs by SOC and PT		X	
Serious AEs by SOC and PT		X	
T Cell Related AEs by SOC and PT		X	
Fatal AEs by SOC and PT		X	
AEs by SOC and PT and Maximum Toxicity Grade		X	X
T Cell Related AEs by SOC and PT and Maximum Toxicity Grade		X	

Lymphodepletion Related AEs by SOC and PT and Maximum Toxicity Grade		X	

For second infusion, no tables will be presented. Only one by subject listing of all AEs (16.2.7.1.1) by SOC and PT and Verbatim will be presented.

4.13.2 Deaths, Serious Adverse Events, and Other Significant Adverse Events

Additional, significant AE summaries that will be provided are:

- Number and percentage of subjects with serious TEAEs
- Number and percentage of subjects with treatment-related serious TEAEs
- Number and percentage of subjects with fatal TEAEs

All summaries will follow the same criteria as mentioned in Section 4.13.1.

Prolonged Cytopenia

Prolonged Cytopenia is defined as Grade 3 or higher Anemia, Thrombocytopenia,Neutropenia, or WBC decreased (leukopenia). The severity is assessed using CTCAE5 criteria Grade 3 or higher the following summaries are to be produced:

- Incidence of Anemia: Hgb < 80 g/L, Thrombocytopenia: Plt < 50 10^9/L, Neutropenia: ANC < 1.0 10^9/L), WBC decreased (leukopenia): WBC < 2.0 10^9/L.

Listing of Lab data for Hemoglobin (g/L), Platelets (10^9/L), ANC (10^9/L), and WBC decreased (10^9/L) between and inclusive of Week 4 and Week 12 will be provided for 1st Infusion and 2nd Infusion separately. The study will use the same assessments for both the first and second infusions.

Data from all the visits included between Week 4 and Week 12 will be mapped to Week 4, Week 8 and Week 12 based on the following reporting window:

- Visit Windowing for Week 4 is based on worst value from day 24 to Day 41 post Tcell infusion Inclusive (week 3.5 to week6).
- Visit Windowing for Week 8 is based on worst value from day 42 to Day 69 post Tcell infusion Inclusive (week 6 to week 10).
- Visit Windowing for Week 12 is based on worst value from day 70 to Day 84 post Tcell infusion Inclusive (week 10 to week 12).

If there are more than one value at the same visit, the worst laboratory value will be displayed.

Table to summarize the proportion of patients who have cytopenia at week 4, 8, 12 will be provided, data associated with 1st Infusion and 2nd Infusion will be presented separately. A by-subject listing will also be provided.

Death

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. Reason for death will be summarized. Number of days since T cell infusion will be reported in the category of death less than 30 days since first T cell infusion, and death greater than or equal to 30 days since first T cell infusion.

A by-subject listing of death will be provided.

4.13.3 Clinical Laboratory Evaluation

Local laboratories will be used for laboratory safety evaluations in this study. For a list of the parameters to be evaluated, see Table 4. Laboratory normal ranges will be provided by the local laboratory. For parameters where an NCI CTCAE v.5.0 scale exists, laboratory results will be graded according to the NCI CTCAE v.5.0 severity grade. For parameters for where an NCI CTCAE v.5.0 scale does not exist, an indicator of whether the value is below, within, or above the normal range will represent severity instead.

All laboratory values will be reported in SI units.

Summaries for each laboratory parameter will be presented by dose group and visit. For by-visit summaries, the first non-missing assessment (including repeat assessments) recorded at each visit will be used. Optional laboratory parameters will not be summarized by dose group, only listed. Separate summaries will be provided for subjects who received second infusion.

For laboratory values reported as a character value, such as <40, will be transformed into numerical values for summary reasons by following the specified guidelines.

Shifts in grade from baseline to the maximum shift(across all visits) will be summarized by dose group.

A by-subject listing of all laboratory data, with abnormal values flagged, will be provided by dose group. This listing will include subject identifier, age, gender, race, and visit, as well as laboratory reference ranges for each parameter.

Table 4 List of Laboratory Parameters

Clinical Chemistry	**Hematology**
Calcium Phosphorus Magnesium Albumin Bilirubin Alanine aminotransferase Aspartate aminotransferase Alkaline phosphatase LDH Sodium Potassium Bicarbonate Creatinine Chloride Glucose Urea	Red cell count Hemoglobin Hematocrit Mean cell volume Mean corpuscular hemoglobin Mean corpuscular hemoglobin concentration Platelet count White blood cell count Lymphocytes, absolute and % Monocytes, absolute and % Neutrophils, absolute and % Eosinophils, absolute and % Basophils, absolute and %
	Coagulation
	Prothrombin Time International Normalized Ratio Activated Partial Thromboplastin Time
Other Tests	**Thyroid Function Tests**
C-reactive protein Ferritin Fibrinogen	Thyroid Stimulating Hormone (TSH) Free T4
Pregnancy Test	**Infectious disease screen**
Serum or Urine	CMV IgG CMV DNA PCR Hepatitis B Surface Antigen Hepatitis B Core Antibody Hepatitis B Viral DNA Hepatitis C Virus Antibody Hepatitis C Virus RNA HIV 1+2 Antibody HTLV 1+2 IgG EBV (EBNA) Treponema IgG
CD3/CD4/CD8	
CD3, absolute and % CD4, absolute and % CD8, absolute and %	

To assess Hy's Law, the number and percentage of subjects with potentially clinically significant post-baseline elevations in hepatic parameters shown in Table 5 below will be summarized by dose group.

A listing of the subjects with potentially clinically significant post-baseline hepatic elevations will be provided. The listing will contain all a subject's values for parameters meeting the criteria.

Table 5. Potentially Clinically Significant Elevations in Hepatic Parameters

ALT-absolute	ALT ≥8xULN
ALT Increase	ALT ≥5xULN but <8xULN persists for ≥2 weeks ALT ≥3xULN but <5xULN persists for ≥4 weeks

Bilirubin[1, 2]	ALT ≥3xULN **and** bilirubin ≥2xULN (>35% direct bilirubin)
INR[2]	ALT ≥3xULN **and** international normalized ratio (INR) >1.5, if INR measured

* ALT = Alanine aminotransferase;

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study intervention if ALT ≥3xULN **and** bilirubin ≥2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, **record the absence/presence of detectable urinary bilirubin on dipstick** which is indicative of direct bilirubin elevations suggesting liver injury.
2. All events of ALT ≥3xULN **and** bilirubin ≥2xULN (>35% direct bilirubin) or ALT ≥3xULN **and** INR >1.5 may indicate severe liver injury **(possible 'Hy's Law') and must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**. The INR stated threshold value will not apply to participants receiving anticoagulants.

4.13.1 Persistence of MAGE-A4^{c1032}T and Replication Competent Lentivirus (RCL) and Cytokine.

Persistence values (i.e., peak persistence) and time to peak persistence will be summarized descriptively (number of subjects, mean, median, standard deviation, minimum and maximum values) by group, overall,. This data will also be listed and displayed graphically with spider plots and box plots by group, overall, and for responders and non-responder.

RCL and persistence results (raw and derived) will be presented by cell dose group and subject in a data listing.

If data permits, persistence values for second infusion will be summarized descriptively and graphically. All persistence data for second infusions will be provided in a listing.

Note 1: The values of persistence that are <xx will be mapped to 1, for instance <50, values that are >xx will be set to xx, for instance >158114.5 will be set to 158114.5. on the applicable outputs.

Note 2: Cytokines: "Fail QC" "Fail Std" "CV>25%" "TNP" "DNR" "CV>30%" "std" "std Fail" impute to '. ' if the values are <xx or >xx then remove the symbols '<' and '>' and present the xx value. Baseline is the first non-missing cytokine value. E.g . Baseline for IL1beta is select the first non missing IL1beta_BL , sort by subject ID and IL1Beta_BL_AD and then select the first value.

4.13.2 Vital Signs, Physical Findings and Other Observations Related to Safety

Vital Signs

Vital sign assessments will be collected in accordance with the schedule of assessments as specified in Table 5 of the study protocol. They will include measurements of diastolic and systolic

blood pressure (mmHg), heart rate (beats per minute), respiration rate (breaths per minute), and body temperature (Celsius).

Summaries for each vital sign parameter will be presented by dose group and visit.

ECG

A 12-lead ECG will be performed in accordance with the schedule of assessments as specified in Table 5 of the study protocol. This assessment will include result findings categorized as normal; abnormal, not clinically significant; abnormal, clinically significant; or unevaluable. The following ECG parameters will be recorded: RR-interval (msec), QRS-interval (msec), PR-interval (msec), QT-interval (msec), QTc-interval (msec), QT-interval corrected using the Frederica correction formula (QTcF) (msec).

Descriptive statistics (n, mean, SD, median, minimum, maximum) for absolute values will be presented by dose cohort.

All ECG parameters will be listed by subject for each dose group and time point.

ECOG Performance Status

In accordance with the schedule of assessments as specified in Table 5 of the study protocol, ECOG performance status will be recorded as follows:

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

ECOG status will be summarized by visit for each dose group and overall.

A by-subject listing will be provided by dose group.

4.14 Other Analyses

CARTOX-10 Assessment

CARTOX-10 assessment results will be listed by subject at baseline (the assessment taken on the same day as, but prior to T cell infusion), and each scheduled post-baseline visits for the mITT population.

The three categories of the CARTOX-10 scores are:

Mild Impairment - total reported CARTOX-10 score of 7-9
Moderate Impairment - total reported CARTOX-10 score of 3-6
Severe Impairment - total reported CARTOX-10 score of 0-2

4.15 Determination of Sample Size

No formal testing of hypotheses has been planned for this study. Therefore, no formal sample size calculations were performed.

4.16 Changes in the Conduct of the Study or Planned Analysis

Protocol Amendment 7 added a radiation therapy sub-study. For the purpose of the CSR, no subjects enrolled in the radiation therapy sub-study arm will be summarized or listed in any tables, listings or figures.

5 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 subjects 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.

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