Adaptimmune LLC

STATISTICAL ANALYSIS PLAN
Protocol Number ADP-01411

IND# 014603

A Phase I/IIa, dual-cohort, two-site, clinical trial evaluating the safety and activity of redirected autologous T cells expressing a high affinity TCR specific for NY-ESO-1 administered post ASCT in patients with advanced myeloma

SPONSOR

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3 List of Abbreviations and Terms

Abbreviation	Description
AE	Adverse Event
ATC-2	Anatomical Therapeutic Chemical 2nd level
ATC-3	Anatomical Therapeutic Chemical 3rd level
BMI	Body Mass Index
BOR	Best Objective Response
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CMV	Cytomegalovirus
CR	Complete Response
CRP	C-reactive Protein
CRS	Cytokine Release Syndrome
CTCAE	Common Toxicity Criteria for Adverse Events
DOR	Duration of Response
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
eCTD	Electronic Common Technical Document
GVHD	Graft Versus Host Disease
ICH	International Conference on Harmonisation
IMWG	International Myeloma Working Group
ITT	Intent-to-treat
KM	Kaplan-Meier
LTFU	Long-Term Follow-Up
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-Treat
NCI	National Cancer Institute
ORR	Objective Response Rate
OS	Overall Survival
PCR	Polymerase Chain Reaction
PCV	Pneumococcal Conjugate Vaccine
PD	Progressive Disease or Relapse
PFS	Progression-Free Survival
PP	Per-protocol
PR	Partial Response
PT	Preferred Term
RCL	Replication Competent Lentovirus
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
sCR	Stringent Complete Response
SD	Stable Disease
SOC	System Organ Class

VGPR	Very Good Partial Response
WHO	World Health Organization

4 Introduction

This statistical analysis plan (SAP) describes the efficacy and safety analyses that will be performed for Study ADP-01411, based on the study protocol Version 12, dated 07Apr2017. The SAP should be used in conjunction with the protocol and electronic case report form (eCRF).

5 Overall Study Design and Objectives

5.1 Study Objectives

5.1.1 Primary Objectives

1. To evaluate the safety and tolerability of autologous genetically modified T cells transduced to express the high affinity NYESO-1 TCR in HLA-A2 subjects.
2. To measure the incidence of graft versus host disease (GVHD) in patients following infusion of TCR modified autologous T cells.

5.1.2 Secondary Objectives

1. To demonstrate product bioactivity, and establish proof of concept and mechanism for the function of gene-modified cells in vivo by evaluating:
   a. Selective migration and engraftment of gene-modified infused cells to the marrow.
   b. Ex-vivo immune functionality and phenotype of infused cells in marrow and periphery.
   c. Modulation of cytokine milieu in marrow and periphery.
   d. Development of an expanded patient immune response against tumor via epitope spreading.
   e. Expression levels of NY-ESO-1 in marrow samples obtained pre- and post-treatment
2. To evaluate the effect of late (Day +100) lenalidomide treatment on the secondary objectives 1a-e above.
3. To evaluate post-transplant cellular and antibody pneumococcal conjugate vaccine (PCV) responses following adoptive transfer of up to $1x10^{10}$ PCV-vaccine-primed and TCR-gene-transduced autologous T cells.
4. To evaluate the clinical response in the NYESO cohort as specified in Rajkumar et al. on behalf of International Myeloma Working Group (IMWG) in 2011 (Rajkumar, 2011) by measuring:
   a. Objective response rate (ORR) at day 42, 100, 180, 270, and 360.
   b. Best objective response (BOR) prior to initiating lenalidomide and at day 360.
   c. Duration of response (DOR) and progression-free survival (PFS).
   d. Overall survival (OS) will be followed in this interventional protocol and continue to be followed in the long-term follow-up protocol, once subjects have transferred.

Initiation of lenalidomide as maintenance treatment will be addressed in a sensitivity analysis.

5.2 Study Endpoints

5.2.1 Primary Endpoint

The primary endpoint for this study is the occurrence of adverse events, per the National Cancer Institute (NCI) Common Toxicity Criteria for Adverse Events (CTCAE) (Version 4) guidelines, including > grade 4 laboratory toxicities at any time from day -40 until year 1. This will include infusional toxicity, and any toxicity probably or definitely related to NYESO-1-c259-T including but not limited to:

a. Fevers
b. Rash
c. Neutropenia, thrombocytopenia, anemia, marrow aplasia
d. Hepatic dysfunction
e. Pulmonary infiltrates or other pulmonary toxicity
f. Development of GVHD

5.2.2 Secondary Endpoints

Secondary endpoints will evaluate correlates of treatment efficacy by measuring clinical response rates to treatment:

a. Progression-free survival (PFS) and duration of response (DOR),
b. Objective response rate (ORR) at day 42, 100, 180, 270 and 360.
c. Best objective response (BOR) prior to initiating lenalidomide and at day 360.
d. Overall survival (OS) will be followed in this interventional protocol and continue to be followed in the long-term follow-up protocol, once subjects have transferred.

5.2.3 Exploratory Endpoints

Exploratory endpoints will evaluate correlates of treatment efficacy by measuring (i) the appearance of target antigen/MHC loss variants upon disease recurrence, as well as (ii) immunological parameters associated with product persistence, bioactivity and functionality.

i. Appearance of target antigen/MHC loss variants upon disease recurrence will be evaluated by quantifying expression of targeted antigens and MHC in marrow samples obtained on disease recurrence, and comparing those values to the pre-treatment (diagnosis) samples. NY-ESO-1 and MHC expression will be evaluated by RNA and/or protein-based assays on tumor samples.
ii. Immunological parameters associated with product bioactivity and functionality will measure selective migration and engraftment of gene-modified infused cells to the marrow post infusion, the ex-vivo immune functionality and phenotype of infused cells in marrow and periphery, the modulation of cytokine milieu in marrow and periphery at baseline, and post T cell infusion and post lenalidomide

treatment as well as the development of an expanded patient immune response against tumor via epitope spreading

5.3 Trial Design and Study Procedures

5.3.1 Study Design

This trial was designed as a dual-cohort study as of Protocol Amendment 12. Study implementation (including study design) is described in detail in Section 3 of the protocol. IND 14603 sponsorship for the investigational product NY-ESO-1^{c259}T was transferred to Adaptimmune. Only the cohort of subjects who are enrolled to receive NY-ESO-1^{c259}T is being summarized here.

Subjects are eligible for the study if they test positive for HLA-A201; are between 18-80 years of age; and have NY-ESO-1 and/or LAGE-1a positive myeloma. Efficacy, safety, and biomarker assessments to be conducted at each visit are outlined in the Schedule of Evaluations in Section 14 (Appendix C) of the protocol.

5.3.2 Treatments and Assignment to Treatment

Drug administration details are described in Section 5 of the protocol.

Per protocol, all subjects will receive high dose melphalan (on Day -2) followed by hematopoietic stem cell transplant on Day 0. On Day +2, subjects receive a dose of NY-ESO-1^{c259}T cells, then are followed for toxicity, antitumor effects, and immune endpoints. The target dose is >0.1-1x10^{10} with a minimum of 0.1-1x10^{9} cells in the final product. At Day 100, subjects will start lenalidomide maintenance.

Subjects who had progressive disease and still express the NY-ESO-1/LAGE1-a antigen may have been eligible to receive a 2nd T cell infusion. The 2nd T cell infusion is described in Section 5.9 of the protocol.

5.4 Sample Size

Sample size computation is described in section 7.3 of the protocol.

6 General Analysis Conventions

In the protocol and eCRF, the date of hematopoietic stem cell transplant is referred to as Day 0 and the date of the T cell infusion is Day +2.

Per Clinical Data Interchange Standards Consortium (CDISC) terminology, the date of T cell infusion will be identified as Day 1 on all tables, listings, and figures. All positive visit days will be properly adjusted to this terminology.

Data collected in the study will be documented using summary tables and subject data listings. Continuous variables will be summarized using descriptive statistics (number of subjects, mean, median, standard deviation, minimum, and maximum). Categorical variables will be summarized using frequencies and proportions. Time-to-event data will be summarized using Kaplan-Meier (KM) methodology using the 25th, 50th (median), and 75th percentiles with associated two-sided 95% confidence intervals (CIs) using the complementary log-log transformation, as well as the proportion of censored observations. The 95% CIs for proportions will be calculated using Clopper-Pearson (exact) and Wilson confidence limits.

Because of the small number of expected subjects receiving a second infusion, only select adverse events tables will be prepared for data on subjects who receive a second infusion. Efficacy data for second infusion subjects will be presented in listings only.

Table 1. Definition of Baseline

Assessment/Test	Visit
Myeloma markers	(Screening) Day -50
Demography Parameters	(Date of Informed Consent) Day -50
Hematology, Chemistry, C-reactive protein (CRP), polymerase chain reaction (PCR), Additional Lab[1]	Most recent value prior to initiating High Dose Melphalan (Day -2)[2]
Vital Signs, Physical Exam, ECOG	Most recent value prior to initiating High Dose Melphalan (Day -2)[2]
ECHO	Most recent value prior to initiating High Dose Melphalan (Day -2)[2]

1 - CMV is only collected before infusion (i.e. only twice for second infusion subjects
2 - High Dose Melphalan may not be used for second infusions. In these cases, baseline for the second infusion will be the most recent value prior to the chemoconditioning regimen (i.e., bortezomib, cyclophosphamide).

In the event of partial or missing dates, the following algorithms will be used (Table 2).

Table 2. Partial or Missing Date Algorithms

Variable	Missing Day	Missing Day, Month	Missing Day, Month, Year
Date of Last Systemic Therapy/Date of Initial Diagnosis	Assign 1	Assign January 1 if prior to date of informed consent, otherwise use date of informed consent	Missing (do not impute)
Adverse Event/Start Date	Assign first day of month unless it is the month of Day -40 visit Otherwise, assign date of Day -40 visit	Assign January 1 unless the year is year of start of Day -40 visit Otherwise, assign date of Day -40 visit	Assign date of Day -40 visit

Adverse Event End Date	Assign the last day of the month or end of study date, whichever is earlier.	Assign December 31 or end of study date, whichever is earlier.	If ongoing, end date is missing. Otherwise, assign end of study date.
Lenalidomide Medication/Start Date	Assign the first day of the month.	Assign date of visit Day 100.	Assign date of visit Day 100.
Lenalidomide Medication/Stop Date	No imputation	No imputation	No imputation

Missing date information for concomitant medication will not be imputed. (Note AE end dates are imputed to facilitate calculation of AE duration, if needed.)

Medical history, adverse events and concurrent procedures will be coded using Medical Dictionary for Regulatory Activities (MedDRA), Version 20 or higher. Prior and concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary (December 2015 or later).

Data for all subjects in the clinical database will be included in the data listings. Calculated (derived) variables will be listed as appropriate. All tables, listings, and figures will be programmed using SAS Version 9.3 or higher.

A list of proposed statistical tables, data listings, and figures is provided in Section 17.

Body mass index (BMI) will be computed as weight in Kg/height in m^2.

6.1 Study Periods

Subjects will be monitored for adverse events for the duration of the intervention protocol (Day -40 visit until relapse/progression or until 1 year, whichever comes first). Subjects who remain disease progression-free beyond Year 1 will only be monitored for delayed adverse events related to the gene transfer aspect of the protocol until disease progression or until transferred into the long-term follow-up protocol (see Section 6.4 of the Protocol). After disease progression, subjects will be rolled over to the long-term follow-up (LTFU) protocol when available at the site.

AEs will be reported for the period corresponding to: Day -40 to end of Intervention Phase. Day -40 corresponds to the day of administration of Prevnar vaccine. AEs will also be reported for the period corresponding to: Day -2 to end of Intervention Phase. Day -2 corresponds to the day of administration of high dose melphalan (Infusion 1) or cyclophosphamide (Infusion 2).

If the date of Day -40 visit/Prevnar is missing, then all AEs prior Day -40 will be listed.

6.2 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. In data listings, dates and study day will be presented. Note: for time-to-event analysis, evaluations will be based on the actual date of the event rather than on the visit on which the event was reported.

7 Analysis Populations

The number of subjects in each study population will be summarized.

7.1 Intent-to-Treat Population

The intent-to-treat (ITT) population will include all subjects who were enrolled in the trial, i.e. all subjects with date of informed consent. The ITT population will be used to assess the efficacy and safety of the T cell therapy regiment.

7.2 Modified Intent-to-Treat Population

The modified intent-to-treat (mITT) population will include all ITT subjects who receive NY-ESO-1c259T cell infusion. The mITT population is the primary analysis population for both safety and efficacy. Because the ITT and mITT populations are the same for this study, only analyses associated with the ITT population will be reported.

7.3 Per-Protocol Population

A per-protocol population (PP) may be included if there are subjects in the mITT population who have protocol deviations that are expected to affect efficacy assessments (e.g. subjects enrolled who do not meet key eligibility criteria) during the trial. Exclusions from the per-protocol population will be identified and documented prior to database lock. If there is no data for exclusion of analysis, PP will not be derived.

8 Subject Disposition

Subject disposition will be summarized for all subjects who entered the study (i.e. signed the informed consent and enrolled in the study) and will include the number of subjects in each population (ITT, mITT, PP if applicable). The number and proportion of subjects who complete the trial, as well as those exiting the interventional phase for each reason specified on the eCRF will also be summarized. A subject who does not receive a second infusion will be considered to have completed the trial when he/she has progression of disease or death, or if the subject remains progression-free at the time of study completion (at the Sponsor's discretion) and is rolled over to the Long Term Follow-up. For subjects who receive a second infusion, completion is defined by their progression (after the second infusion) or death, or if the subject remains progression-free at the time

of study completion (at the Sponsor's discretion) and is rolled over to the Long Term Follow-up.

Reasons for early discontinuation of an investigational phase (Infusion 1 or 2) are:

- Disease progression
- Unacceptable toxicity and other safety reasons
- Death
- Investigator discretion
- Subject withdrew consent
- Protocol deviation
- Lost to follow-up
- Termination by Sponsor
- Failed manufacture of cell product
- Pregnancy
- Failed to meet eligibility criteria for the second infusion
- Study completion per sponsor decision

T-cell infused subjects excluded from analysis populations will be presented in a data listing. This listing will not be produced if there are no such subjects.

9 Protocol Deviations

Subjects will be excluded from the per-protocol population if they have protocol deviations expected to affect efficacy assessments. Protocol deviations will be presented by subject in a data listing. No per-protocol population analysis will be pursued if there no such deviation data that affect efficacy assessments.

10 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized and presented by subject in data listings.

10.1 Demographic Characteristics

Demographic and baseline characteristics at study entry will be summarized for the ITT population. Variables to be summarized are:

- Continuous variables
  - Age (years) at time of informed consent
  - Weight (kg, converted from pounds if necessary)
  - Height (cm, converted from inches if necessary)
  - BMI [(weight in kg)/(height in m)^2]
- Categorical variables

- Sex
- Race
- Ethnicity
- NY-ESO-1 status
- LAGE-1a status
- HLA status (HLA-A1+, HLA-A2+, Other)
- ECOG performance status at baseline

10.2 Medical History

Medical history information will be presented by subject in a data listing.

10.3 Prior Cancer Therapy

Prior oncology treatment will be presented by subject in a data listing.

11 Statistical Methods for Safety Endpoints

The primary endpoint of the study is occurrence of adverse events, per the NCI CTCAE (Version 4) guidelines, including > grade 4 laboratory toxicities at any time from Day -40 until Year 1. This will include infusional toxicity, and any toxicity possibly, probably or definitely related to NYESO-1-c259-T including but not limited to:

a. Fevers
b. Rash
c. Neutropenia, thrombocytopenia, anemia, marrow aplasia
d. Hepatic dysfunction
e. Pulmonary infiltrates or other pulmonary toxicity
f. Development of GVHD

See Appendix 3 for a listing of AE of special interest.

NOTE: Transplant-related toxicities, typically occurring within a month post-transplant, are excluded as study related adverse events. This will not require programmatic exclusions, the eDC data will not reflect such events.

In addition to probably and definitely related events, possibly related events will also be considered.

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

Potentially Clinically Significant Elevations in Hepatic Parameters

Parameter*	Criterion
ALT, AST and Total Bilirubin Elevations	≥3 xULN AST and/or ALT and ≥2 xULN total BIL
	≥3 xULN AST and/or ALT and ≥1.5 xULN total BIL
ALT Elevations	≥20 xULN
	≥10 xULN
	≥5 xULN
	≥3 xULN
Total Bilirubin Elevations	>2 xULN
	>1.5 xULN

*ALT = Alanine aminotransferase, ALK = Alkaline Phosphatase, AST = Aspartate aminotransferase, BIL = Total bilirubin, ULN = upper limit of normal.

Other safety assessments include physical exams, vital signs, and concomitant medications.

All safety data will be included in data listings. Descriptive statistics will be provided for exposure, safety, and laboratory assessments. Continuous variables will be summarized using descriptive statistics (number of subjects, mean, median, standard deviation, minimum, and maximum), while categorical data will be summarized using frequency counts and percentages.

11.1 Adverse Events

All adverse events (AEs) will be tabulated by MedDRA system organ class (SOC) in alphabetic order and by preferred term (PT) in decreasing order of frequency within each SOC for the two time periods described in Section 6.1, unless otherwise indicated. The two time periods will be presented as separate columns within the statistical tables. Other summaries of AEs will be by preferred term, listed in order of decreasing frequency. MedDRA PTs identified as 'like/synonymous', such as Decreased neutrophils, Neutrophils low, and Neutropenia, will be identified by the Adaptimmune Safety group and summarized (Appendix 2). The number and percent of subjects reporting any AEs will be tabulated by system organ class and preferred term. AEs will be further classified by severity, relationship to treatment and seriousness in tabulation.

The number and percentage of subjects who experienced at least one AE will be summarized overall and for each SOC and each PT. The proportion will be based on the number of subjects in the relevant population. Each subject will contribute at most one count per summarization category. In other words, if a subject has more than one AE with the same PT, the subject will be counted only once for that PT. Similarly, if a subject has more than one AE for a SOC, the subject will be counted only once in that SOC, listing out all the PTs.

AEs will be graded according to the NCI CTCAE Version 4. AE toxicity grade will be classified into 5 categories: Grade 1 = mild, Grade 2 = moderate, Grade 3 = severe, Grade 4 = life threatening and Grade 5 = fatal. If a subject has multiple occurrences of the same SOC or PT, then only the most severe event will be summarized in the tables for that SOC and PT.

The relationship of the AEs to the T-cell infusions will be classified into the following categories: definite, probable, possible, unlikely, and unrelated (Note: there is also an "unknown" option on the eCRF but this response will not be summarized). AEs will be summarized in the tables as 'related' or 'not related' and listings will display all categories. Treatment-related AEs include definitely related, probably related, possibly related, and unlikely. If a subject has multiple occurrences of the same SOC or PT, only the most related event will be summarized in the tables for that SOC and PT.

No formal hypothesis-testing analysis of AE incidence rates will be performed. All reported AEs will be listed in data listings, with a separate listing for AEs associated with a second T cell infusion. By-subject listings also will be provided for all serious AEs; the listings will identify which AEs are associated with the first T cell infusion and which are associated with the second T cell infusion. In addition, deaths and cause of death will be presented in a data listing.

Additionally, by-subject listings for subjects experiencing AEs of GVHD will be provided as data permit (MedDRA preferred terms are listed in Appendix 2).

Adverse Event Summaries

The number and proportion of subjects with the following categories of AEs will be summarized in tables by PT for all summaries and by SOC and PT for all AEsfor the ITT dataset, unless otherwise indicated.

- Any AE
- Any AE by toxicity grade
- Any treatment-related AE
- AE of special interest by toxicity grade (See Appendix 3 for a listing of AE of interest and associate PT's)
- Any SAE
- Any treatment-related SAE
- Adverse events grouped by similarity of preferred terms (by synonym and PT) (See Appendix 2 for a listing of PTs associated with each synonym)

11.2 Study Drug Exposure

The total number of transduced T cells (derived using the formula: transduction efficiency x total number of T cells), along with the transduction efficiency and total

number of T-cells infused, will be summarized for the first and second T-cell infusion for the ITT population using descriptive statistics. The number of transduced cells will be listed, including for subjects with a second T cell infusion.

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

11.3 Laboratory Tests

Laboratory tests will be presented in a subject data listing.

11.3.1 Clinical Laboratory Tests

Quantitative clinical laboratory results for hematology, clinical chemistry, and myeloma markers will be listed by subject. Refer to Appendix 1 for a list of safety laboratory tests by category.

Myeloma markers, including bone marrow aspirate (% plasma cells in marrow aspiration), bone marrow biopsy (% plasma cells in marrow biopsy), and marrow cytogenetics (% abnormal clone), will be listed by subject.

Shift tables that present changes from baseline to worst post-baseline values relative to NCI CTCAE version 4 classification ranges will be produced for laboratory parameters with quantitative CTCAE criteria.

All laboratory parameters, with investigator assessment of clinical significance, will be included in data listings.

11.3.2 Persistence of NY-ESO-1c259T and Replication Competent Lentivirus (RCL)

Spider plots will be used to graphically summarize persistence over time for each subject by responders and non-responders at day 42, 100, 180, 270, and 360. Maximum persistence during the study and time to maximum persistence will be summarized overall and for responders and non-responders using descriptive statistics and boxplots. The proportion of subjects who are RCL positive will be summarized for the ITT population.

Persistence results and RCL (if data permit) will be presented by subject in a data listing.

11.4 Vital Signs

Vital signs will be presented by subject in a data listing.

11.5 Electrocardiograms

All electrocardiogram and ECHO results will be presented by subject in data listings.

11.6 Eastern Cooperative Oncology Group (ECOG) Performance Status

ECOG performance status results will be summarized at baseline, each scheduled post-baseline visit with counts and proportion of subjects with each score for the ITT population.

11.7 Concomitant Medications

All concomitant medication data will be listed by subject.

12 Statistical Methods for Efficacy

The study objectives are described in Section 1 and the study endpoints are described in Section 7.2 of the protocol.

The primary analysis population for efficacy endpoints will be the ITT population because the ITT and mITT populations are the same for this study.

12.1 Efficacy Analysis of Binary Endpoints

Tumor response will be assessed by IMWG 2011 criteria. IMWG 2011 response categories are stringent complete response (sCR), complete response (CR), very good partial response (VGPR), partial response (PR), stable disease (SD), and progressive disease or relapse (PD). The categorical efficacy endpoints are objective response rate (ORR) and best objective response (BOR). ORR is defined as the percentage of subjects who have a positive response (PR, VGPR, CR, or sCR) in accordance with (IMWG; Rajkumar, 2011). This determination is made by the Investigator and entered as such (i.e., PR, VGPR etc.) in the eDC.

BOR is defined as the best response experienced by the subject from first assessment of positive response (PR, VGPR, CR, or sCR) until some specified time point (e.g. initiation of lenalidomide and Year 1). For example, BOR prior to initiating lenalidomide will be assessed as the best response experienced by the subject from first assessment of positive response (PR, VGPR, CR, or sCR) up to the initiation of lenalidomide.

For both ORR and BOR endpoints, subjects with unknown or missing response will be treated as non-responders.

For BOR prior to initiating lenalidomide, if the subject had no lenalidomide treatment, Day 100 will be used for the subject.

ORR will be summarized using Clopper-Pearson 95% (exact) confidence intervals. In addition, 95% confidence intervals will also be computed using the Wilson method. Frequency table summary (n (%) will be obtained for BOR up to initiating lenalidomide, Day100 and Year 1 respectively, as well for each IMWG 2011 responses for each visit up to Year 1 (Day 360).

12.2 Efficacy Analysis of Time to Event Endpoints

The time to event efficacy endpoints are progression free survival (PFS), overall survival (OS), and duration of response (DOR).

PFS is the interval between T-cell infusion and the earliest date of disease progression or death due to any cause. Subjects without a documented date of disease progression or death will be censored at the date of the last study assessment for PFS.

OS is the interval between T-cell infusion and death. Subjects who are lost to follow-up or still alive will be censored at the date of last contact for OS.

DOR is defined as the time from the initial date of response to the date of the progressive disease (as determined by the Investigator) or death. Subjects who are still alive and who do not have a documented disease progression will be censored at the date of the last study assessment for DOR.

Time to event endpoints will be summarized and displayed graphically using Kaplan-Meier methodology to estimate the median, and the 25th and 75th percentiles. Two-sided 95% confidence intervals will be produced using the complementary log-log method. The proportion of censored observations will also be summarized. PFS, OS and DOR results will be presented in one analysis results table for easier comparisons.

12.3 Exploratory Efficacy Analyses

Exploratory endpoints will evaluate correlates of treatment efficacy by measuring as data permit:

- The appearance of target antigen/MHC loss variants upon disease recurrence.
- Immunological parameters associated with product persistence, bioactivity, and functionality.

This data will not be analyzed as part of this statistical analysis plan.

13 Statistical/Analytical Issues

13.1 Pooling of Centers in Multi-Center Studies

Data will not be summarized by study center or for groupings of study centers.

13.2 Multiple Comparisons/Multiplicity

No adjustments for multiple comparisons or multiplicity are planned.

13.3 Examination of Subgroups

No subgroup analyses are planned.

14 Quality Control

All data displays and analyses will adhere to the International Conference on Harmonisation (ICH) *Harmonized Tripartite Guideline: Structure and Content of Clinical Study Reports (ICH Topic E3)*.

Adaptimmune will review all tables, listings, and figures prior to final database lock. Final SAS datasets, programs and outputs will be transferred to Adaptimmune at project completion.

15 Tables and Listings Conventions

Mock-ups for statistical tables and listings will be provided. Final formats for the statistical tables and listings may deviate from these mock-ups upon agreement with Adaptimmune. Footnotes will be used as needed to clarify the information that is presented in the tables and listings. Unless otherwise requested by Adaptimmune, the term ‘subject’ will be used in all tables and listings, in accordance with CDISC standards. Basic demographic information (age/gender) will be presented along with subject id for each listing. Similar endpoints (e.g, all lab tests, all time to events endpoints etc.) should present in one listing or table for completeness or comparisons.

The general layout of tables and listings will be as follows:

Adaptimmune LLC Page x of y
Protocol: ADP-01411 Run Date: DDMMMYY -HH:MM
Clinical Study Report

Listing 16.2_x (or Table 14.x_x)

<Title>

<Population>

Col 1 Col 2 Col 3 etc

<Any footnotes>

File Name: <pathname for SAS program>

All tables and listings will use landscape orientation. Margins will be at least 2.0 cm at the top and bottom and at least 0.8 cm on the left and right, excluding headers and footnotes, in accordance with electronic Common Technical Document (eCTD) guidelines. Font will be Courier, unless otherwise specified, with an 8-point font size in most cases. Page numbering will be sequential within each table, listing, and figure. Column headers should be in initial capital letters. Units for numeric data will be included when appropriate.

Tables and data listings will be created from different SAS programs. A single program may produce multiple tables or multiple data listings from the same dataset (e.g. all clinical chemistry data listings may be generated by a single program).

15.1 Statistical Table Conventions

Mock-ups for statistical tables will include headers, title numbers, titles, column headers and footers, and a proposed layout for the display of data. The final decision on the precision (i.e. number of decimal places) for presentation of descriptive statistics will be made by Adaptimmune after review of draft statistical tables and before database freeze.

15.2 Data Listing Conventions

Mock-ups for data listings will include headers, title numbers, titles, column headers, and footnotes as appropriate. Data listings will provide all data collected on the corresponding eCRF page or provided by external vendors, unless otherwise indicated.

In general, data listings should include all subjects with data. However, if only subjects who meet a certain condition are listed (e.g., subjects with SAEs) and no subjects meet the condition, the data listing will so indicate.

The sort order for data presented in data listings will be subject ID, unless otherwise requested by Adaptimmune. Within a subject, data will be listed in chronological order. Whenever possible, formatted values will be displayed (i.e., decoded). Where applicable, calendar date and study day of evaluations/events will be provided in the data listings.

Basic demographic information (age, gender) should present along with subject id for each listing.

16 References

Rajkumar SV, Harousseau J-L, Durie B, Anderson KC, Dimopoulos M. et al. Consensus recommendations for the uniform reporting of clinical trials: report of the International Myeloma Workshop Consensus Panel 1. Blood 2011; 117(18): 4691-5.

17 Preliminary List of Tables, Listings, and Figures to Be Programmed

17.1 Statistical Tables

Table Number	Table Title	Analysis Population
14.1.1	Subject Enrollment and Disposition	
14.1.2	Demographic and Baseline Characteristics	ITT
14.2.1	Estimates of Objective Response Rate by Time Points of Interest	ITT
14.2.2	Summary of Best Objective Response and IMWG 2011 Response by Time Points of Interest	ITT
14.2.3	Kaplan-Meier Estimate of Duration of Response, Progression-Free Survival and Overall Survival	ITT
14.3.1.1	Summary of T Cell Infusions	ITT
14.3.1.2	Overall Summary of Adverse Events	ITT
14.3.1.3.1	Incidence of Adverse Events by System Organ Class and Preferred Term	ITT
14.3.1.3.2	Incidence of Adverse Events by Preferred Term	
14.3.1.4	Incidence of Adverse Events Grouped by Similarity of Preferred Terms by Synonym and Preferred Term	ITT
14.3.1.5	Incidence of Adverse Events of Special Interest by Toxicity Grade and Preferred Term	ITT
14.3.1.6	Incidence of Adverse Events by Toxicity Grade and Preferred Term	ITT
14.3.1.7	Incidence of Adverse Events Related to T cell Therapy by Preferred Term	ITT
14.3.2.1	Incidence of Serious Adverse Events by Preferred Term	ITT
14.3.2.2	Incidence of Serious Adverse Events Related to T Cell Therapy by Preferred Term	ITT
14.3.4.1	Shifts from Baseline to Worst Post-Baseline NCI-CTCAE Grade for lab tests	ITT
14.3.4.2	Shifts from Baseline to Worst Post-Baseline NCI-CTCAE Grade for Chemistry Parameters	ITT
14.3.4.3	Number and Proportion of Subjects with Potentially Clinically Significant Hepatic Post-	ITT

Table Number	Table Title	Analysis Population
	Baseline Results for the Post-lymphodepletion Period	
14.3.4	Maximum Persistence and Time to Maximum Persistence for Responders, Non-responders, and Overall	ITT
14.35	Summary of ECOG Performance Status at Each Visit	ITT

17.2 Data Listings

Number	Title
16.2.1	Subject Disposition
16.2.2 Protocol Deviations	
16.2.2	Protocol Deviations
16.2.3 Subjects Excluded from Efficacy and Safety Analyses	
	No table needed (no subjects excluded)
16.2.4 Demographic Data	
16.2.4.1	Demographics and Baseline Characteristics
16.2.4.2	Medical History
16.2.4.3	Myeloma Diagnosis History
16.2.4.4	Diagnostic Criteria for Myeloma at Screening
16.2.4.5	Prior Oncology Treatment
16.2.5 Study Drug Administration	
16.2.5.1	Procedure and Treatment Dates for Each Subject
16.2.5.2	PCV (Previnar-13) Immunization
16.2.5.3	Lymphodepleting Chemotherapy
16.2.5.4	Stem-Cell Infusion and Bone Marrow Transplant
16.2.5.5	T Cell Infusion
16.2.5.6	Lenalidomide Treatment
16.2.6 Individual Efficacy Response Data	
16.2.6.1	Myeloma Markers
16.2.6..2	Bone Marrow Aspiration and Biopsy

Number	Title
16.2.6.3	Radiology Tests
16.2.6.4	IMWG 2011 Response Assessments at Each Visit
16.2.6.5	Duration of Response, Progression-Free Survival and Overall Survival
16.2.7 Adverse Event Listings	
16.2.7.1	Adverse Events
16.2.7.2	Adverse Events for Second T-Cell Infusion
16.2.7.3	Serious Adverse Events
16.2.7.4	Deaths
16.2.8 Listings of Individual Laboratory Measurements	
16.2.8.1	Laboratory Test Results for Chemistry and Hematology Parameters
16.2.8.2	Listing of CD3, CD4, and CD8 Counts and Findings
16.2.8.3	Replication Competent Lentivirus (RCL)
16.2.8.4	Persistence
16.2.8.5	Pregnancy Test Results
16.2.8.6	Vital Signs
16.2.8.7	ECOG Performance Status
16.2.8.8	Electrocardiogram
16.2.8.9	Concomitant Medications
16.2.8.10	Cardiac Stress Test and Echocardiogram
16.2.8.11	Pulmonary Function Test
16.2.8.12	Infectious Disease Testing
16.2.8.13	Long Term Follow-up Events

17.3 Figures

Number	Figure Title	Analysis Population
1	Kaplan-Meier Plot of Duration of Response	ITT
2	Kaplan-Meier Plot of Progression-Free Survival	ITT
3	Kaplan-Meier Plot of Overall Survival	ITT
4	Patient Response Profile	ITT
5	Boxplots for Maximum Persistence by Responders vs. Non-Responders Prior to Initiation of Lenalidomide and Other Visits Up to Year 1	ITT

Number	Figure Title	Analysis Population
	[All import events/milestones for a patient since first infusion will be marked on a bar chart (by different color and symbols): PD, initiation of lenalidomide, PD, death, Second infusion, IMWG response and duration etc]	
6	Spider Plots for Persistence Results over Time for Responders vs. Non-Responders up to Year 1	ITT

Appendix 1. Laboratory Tests by Category

Myeloma Markers

- SPEP
- Mono Protein Immuno
- UPEP
- IgG
- IgA
- IgM
- Beta 2-Microglobulin
- C-Reactive Protein
- Serum Free Kappa Light Chain
- Serum Free Lambda Light Chain
- K/L Ratio

Hematology

- WBC
- RBC
- Hemoglobin
- Hematocrit Count
- Platelet Count
- Absolute Neutrophil Count
- Absolute Lymphocyte Count
- Absolute Monocyte Count
- Absolute Eosinophil Count
- Absolute Basophil Count

Chemistry

- Glucose
- BUN
- Creatinine
- Sodium
- Potassium
- Chloride
- Bicarbonate
- Calcium
- Total Protein
- Albumin
- Total Bilirubin
- Alkaline Phosphatase
- Aspartate Aminotransferase
- Alanine Aminotransferase

CD Counts
- CD3
- CD4
- CD8

Bone Marrow
- Plasma Cells in Marrow Aspiration
- Plasma Cells in Marrow Biopsy
- Marrow Cytogenetics

Infectious Disease Test
- HIV Test
- HTLV 1/2 Test
- Hepatitis B Test
- Hepatitis C Test
- CMV Test

Pregnancy Test
- Beta hcG Test
- Urine Pregnancy Test

Additional Labs
- Troponin

Appendix 2. List of PTs to Be Combined

The following synonyms will be combined under the PT as shown below. The combined term will be used when reporting AE data in tables by PT. Synonymous terms will be combined regardless of body system. The AE listing will not combine these PTs but list them out as they are reported.

Synonym	**MedDRA Preferred Terms (System Organ Class)**
Anaemia/RBC decreased	Anaemia (Blood and lymphatic system disorders)
Cytokine Release Syndrome (CRS)	Cytokine Release Syndrome (Immune System Disorders) Cytokine Storm (Immune System Disorders)
Graft Versus Host Disease (GVHD)	Acute graft versus host disease Acute graft versus host disease in intestine Acute graft versus host disease in liver Acute graft versus host disease in skin Chronic graft versus host disease Chronic graft versus host disease in intestine Chronic graft versus host disease in liver Chronic graft versus host disease in skin Engraftment syndrome Graft versus host disease Graft versus host disease in eye Graft versus host disease in gastrointestinal tract Graft versus host disease in liver Graft versus host disease in lung Graft versus host disease in skin Transfusion associated graft versus host disease

Synonym	MedDRA Preferred Terms (System Organ Class)
Leukopenia/WBC decreased	White blood cell count decreased (Investigations) Leukopenia (Blood and lymphatic system disorders)
Lymphopenia/Lymphocyte count decreased	Lymphocyte count decreased (Investigations) CD4 lymphocytes decreased (Investigations)
Neutropenia/Neutrophil count decreased	Neutrophil count decreased (Investigations) Neutropenia (Blood and lymphatic system disorders)
Rash/Rash maculo-papular/Genital rash	Rash maculo-papular (Skin and subcutaneous tissue disorders) Rash (Skin and subcutaneous tissue disorders) Genital rash (Reproductive system and breast disorders) Rash erythematous
Thrombocytopenia/Platelet count decreased	Platelet count decreased (Investigations) Thrombocytopenia (Blood and lymphatic system disorders)

Note: Erythema multiforme (Skin and subcutaneous tissue disorders) is not going to be included in rash category per pharmacovigilance request.

Appendix 3. List of AEs of Special interest

The following is the synonyms of AEs of special interest will be combined under the PT as shown below. Note the AE of special interest groups may overlap to each other, i.e. one PT may be accounted for multiple AE of special interest groups.

AEs of Special Interest	**MedDRA Preferred Terms**
Development of GVHD	Graft versus host disease
	Graft versus host disease in gastrointestinal tract
	Graft versus host disease in skin
Fevers	Febrile neutropenia

	Pyrexia
Hepatic dysfunction	Alanine aminotransferase increased
	Aspartate aminotransferase increased
	Blood alkaline phosphatase increased
	Blood bilirubin increased
	Hepatic infection
Neutropenia, thrombocytopenia, anemia, marrow aplasia	Anaemia
	Leukopenia
	Lymphocyte count decreased
	Neutropenia
	Neutrophil count decreased
	Platelet count decreased
	Thrombocytopenia
	White blood cell count decreased
Pulmonary infiltrates or other pulmonary toxicity	Cough
	Dyspnoea
	Hypoxia
	Pneumonia
	Pneumonitis
	Pulmonary oedema
	Rales
	Tachypnoea
	Upper-airway cough syndrome
	Wheezing
Rash	Erythema
	Pharyngeal erythema
	Rash
	Rash erythematous

	Rash maculo-papular
Potential symptom of GVHD	Abdominal distension
	Abdominal pain
	Alanine aminotransferase increased
	Aspartate aminotransferase increased
	Blood alkaline phosphatase increased
	Blood bilirubin increased
	Colitis
	Diarrhoea
	Erythema
	Graft versus host disease
	Graft versus host disease in gastrointestinal tract
	Graft versus host disease in skin
	Mouth ulceration
	Mucosal inflammation
	Nausea
	Oedema peripheral
	Oesophagitis
	Oral mucosal blistering
	Peripheral swelling
	Pruritus
	Rash
	Rash erythematous
	Rash maculo-papular
	Rectal haemorrhage
	Skin disorder
Potential symptom of CRS	Alanine aminotransferase increased
	Aspartate aminotransferase increased

	Confusional state
	Dyspnoea
	Graft versus host disease in gastrointestinal tract
	Headache
	Hypotension
	Hypoxia
	Nausea
	Pyrexia
	Rash
	Rash erythematous
	Rash maculo-papular
	Sinus tachycardia
	Tachycardia
	Tachypnoea
	Unresponsive to stimuli
	Ventricular tachycardia
	Vomiting