PROTOCOL NUMBER ADP-0055-001

A PHASE 1 DOSE ESCALATION STUDY TO ASSESS SAFETY AND EFFICACY OF ADP-A2M4CD8 IN HLA-A2+ SUBJECTS WITH MAGE-A4 POSITIVE TUMORS

PROTOCOL V1.0

DATE: 15 APR 2019

INVESTIGATOR PROTOCOL AGREEMENT PAGE

Protocol Title: A Phase 1 Dose Escalation Study To Assess Safety And Efficacy Of ADP-A2M4CD8 In HLA-A2+ Subjects With MAGE-A4 Positive Tumors

I, the undersigned, have reviewed the protocol, including the appendices, and I will conduct the clinical study as described and will adhere to International Council for Harmonization (ICH) tripartite guideline E6 (R2): Guideline for Good Clinical Practice (GCP) and all the ethical and regulatory considerations stated. I have read and understood the contents of the ADP-A2M4CD8 Investigator's Brochure.

Investigator Name	
Investigator Title	
Investigator Site and Address	
Investigator Signature	
Date	

CLINICAL STUDY PROTOCOL

Title: A Phase 1 Dose Escalation Study To Assess Safety And Efficacy Of ADP-A2M4CD8 In HLA-A2+ Subjects With MAGE-A4 Positive Tumors

Product Name: ADP-A2M4CD8

Protocol Number: ADP-0055-001

IND Number: 18950

EUDRA Number: XXXXXXXX

DATE OF ORIGINAL PROTOCOL 15-APR-2019

Amendment Number	Date	Reason for Change
Version 1.0	15-APR-2019	Original version

CONFIDENTIALITY STATEMENT

DECLARATION

This study will be conducted in compliance with ICH Good Clinical Practice (GCP), all applicable subject privacy requirements, and the guiding principles of the current version of the Declaration of Helsinki (with amendments), and in accordance with local legal and regulatory requirements.

RESPONSIBLE SPONSOR STUDY PHYSICIAN/SPONSOR INFORMATION PAGE

Sponsor Signatory

[redacted]

15 April 2019

Date

Responsible Study Physician/SAE Contact Information

[redacted]

Sponsor Details:

Adaptimmune LLC
351 Rouse Blvd
Philadelphia, PA 19112
USA

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1. PROTOCOL SUMMARY

1.1. Synopsis

Title A Phase 1 Dose Escalation Study To Assess Safety And Efficacy Of ADP-A2M4CD8 In HLA-A2+ Subjects With MAGE-A4 Positive Tumors	
Short Title	ADP-A2M4CD8 in HLA-A2+ Subjects with MAGE-A4 Positive Tumors
Protocol Number	ADP-0055-001
Phase	1
Methodology	The study design is a Phase 1 dose escalation study using a modified 3+3 design, followed by Expansion to characterize safety and tolerability and assess antitumor activity across multiple tumor types. Subjects with any of the tumor types listed under inclusion criterion 4 will be pre-screened through Adaptimmune Screening Protocol (ADP-0000-001, NCT02636855) to determine appropriate human leukocyte antigen (HLA) and tumor antigen status. Only subjects with the required HLA-A*02 allele and whose tumor expresses the MAGE-A4 antigen above the cut-off are eligible to undergo further screening to meet the remaining eligibility criteria for enrollment on this study. Enrolled subjects will undergo leukapheresis for the collection of autologous cells for processing and manufacture into the ADP-A2M4CD8 Investigational Product (IP). Leukapheresis should be performed as soon as possible after the subject is determined to be eligible for study participation. Prior to the administration of lymphodepleting chemotherapy all eligibility criteria will be reconfirmed and the Baseline tumor assessment obtained. When the ADP-A2M4CD8 cells are available at the site, subjects will undergo lymphodepleting chemotherapy with fludarabine and cyclophosphamide followed by infusion of ADP-A2M4CD8 on Day 1. Subjects may be hospitalized for the lymphodepleting chemotherapy at the discretion of the Investigator. During dose escalation, it is required that the T-cell infusion is given as an inpatient procedure and that subjects are hospitalized for at least 72 hours following T-cell infusion. This allows for close monitoring of post-infusion adverse events (AEs) during the dose escalation phase of the study. The subject may be discharged thereafter if medically stable at the discretion of the Investigator. Subjects will have the following study visits: Screening, Leukapheresis, Baseline, Lymphodepleting Chemotherapy (Day -5 through Day -2), T-cell infusion (Day 1) and immediate post infusion monitoring (Day 1 through Day 8), weekly visits until Week 4 post-infusion, and then 6, 8, 12, 16, and 24 weeks and every 3 months thereafter until disease progression.

	Investigators will assess tumor response according to response evaluation criteria in solid tumors (RECIST) v1.1 for clinical decision making. Subjects who have a confirmed response (or clinical benefit ≥4 weeks after the first T-cell infusion) following the initial infusion and whose tumor continues to express the MAGE-A4 antigen target may be eligible for a second infusion. Eligible subjects may receive a second infusion during the Expansion phase of the study, after the subjects in Group 3 have cleared the DLT period. Once disease progression is established, subjects may either enter the Long-Term Follow-Up (LTFU) phase or remain in the Interventional Phase to potentially receive a second infusion. After the Interventional Phase, subjects will enter the LTFU Phase of the study to continue monitoring for potential gene therapy-related delayed AEs, in accordance with FDA and EMA requirements. LTFU monitoring starts from the T-cell infusion and continues for up to 15 years after the last T-cell infusion. LTFU assessments will be collected in the Interventional Phase until the subject enters the LTFU Phase. A subject will be considered to have ended the study when he/she has been followed for 15 years from the time of the last T-cell infusion or discontinued the study for any reason. The study will be considered complete when all subjects complete 15 years of follow-up, die, or withdraw early from the study.
Study Duration	Enrollment is expected to be completed in approximately 18 months. The study will be considered complete when all subjects complete 15 years of follow-up, die or withdraw early from the study.
Study Center(s)	The study will be conducted at approximately 15 sites. Additional sites may be added at the discretion of the Sponsor.
Number of Subjects	Up to eighteen (18) subjects will be included in the dose escalation phase, with up to thirty (30) subjects total being treated in the study inclusive of the dose escalation and Expansion phases to characterize safety and antitumor activity.

Objectives	**Endpoints**
Primary: To evaluate the safety and tolerability of autologous genetically modified T cells (ADP-A2M4CD8) in subjects with HLA-A*02 and MAGE-A4 positive inoperable locally advanced or metastatic tumors	• Incidence of dose-limiting toxicities (DLTs) and determination of optimally tolerated dose range, adverse events (AEs), and serious adverse events (SAEs) • Replication Competent Lentivirus (RCL) • T cell Persistence and Insertional oncogenesis (IO)
Secondary: To evaluate the antitumor activity of autologous genetically modified T cells	• Overall Response Rate (ORR) based on confirmed responses (CR/PR) by RECIST v1.1 • Best overall response (BOR)

(ADP-A2M4CD8) in HLA-A*02 subjects with MAGE-A4 positive inoperable locally advanced or metastatic tumors	• Time to response (TTR) • Duration of response (DoR) • Duration of stable disease (DoSD) • Progression- free survival (PFS) • Overall survival (OS)
[redacted]	
Inclusion Criteria	1. Subject (or legally authorized representative) has voluntarily agreed to participate by giving written Informed Consent in accordance with ICH GCP guidelines and applicable local regulations. 2. Subject has agreed to abide by all protocol-required procedures including study- related assessments, and management by the treating institution for the duration of the study including LTFU. 3. Age ≥18 years at the time the Pre-screening Informed Consent is signed. 4. Histologically or cytogenetically confirmed diagnosis of any one of the following cancers: (A) urothelial cancer), (B) melanoma, (C) ovarian cancer, (D) esophageal (E) esophagogastric junction (EGJ) cancer, (F) gastric cancer, (G) non-small cell lung carcinoma (NSCLC) (H) head and neck (I) synovial sarcoma or (J) myxoid/round cell liposarcoma (MRCLS). 5. Measurable disease according to RECIST v1.1 prior to leukapheresis and lymphodepletion.

	6. Subject must receive ADP-A2M4CD8 as the next therapy following leukapheresis. Subjects may receive bridging therapy during the period in which the subject is awaiting the manufacturing of ADP-A2M4CD8 but must adhere to the mandatory washout periods (Section 5.3) and must have measurable disease prior to receiving ADP-A2M4CD8. 7. Subject has the following disease-specific requirements for their tumor type. NOTE: bridging therapy is not considered a prior systemic therapy). a. Urothelial Carcinoma – Histologically or cytologically confirmed urothelial carcinoma (including mixed histologies of urothelial carcinoma with elements of other subtypes) of the renal pelvis, ureter, bladder, or urethra with metastatic or unresectable locally advanced disease – Prior therapy requirements: – Subjects must have received or refused 1 prior platinum-based therapy for the treatment of metastatic or locally advanced unresectable disease. – Subjects who are not eligible for a platinum-containing regimen or who have progressed on a platinum-containing regimen may have received an anti-PD-l/PD-L1 checkpoint inhibitor. – Subjects may have received no more than three prior systemic regimens which may include investigational therapies. b. Melanoma – Histologically or cytologically confirmed melanoma with metastatic or unresectable locally advanced disease – Prior therapy requirements: – Subjects must have received a BRAF inhibitor as monotherapy or in combination with a MEK inhibitor for *BRAF* V600E mutant melanoma – Subjects must have received or refused an anti-PD-1/ PD-L1 as monotherapy or in combination with an anti-CTLA-4 inhibitor – Subjects may have received no more than three prior systemic regimens which may include investigational therapies c. Ovarian Carcinoma – Histologically or cytologically confirmed ovarian carcinoma (including epithelial ovarian, primary peritoneal, or fallopian tube carcinoma) with disease progression – Prior therapy requirements: – Subjects must have received no more than 3 prior systemic therapies which may include investigational therapies.

	– One regimen must have been a prior platinum-based chemotherapy regimen for primary disease, possibly including intra-peritoneal therapy, consolidation, biologic/targeted (non-cytotoxic agents, or extended therapy (maintenance/consolidation) administered after surgical or non-surgical assessment. Maintenance therapy is not considered a prior systemic therapy. – Subjects must have progressed ≤12 months after completion of their last platinum-based chemotherapy. The number of months (platinum-free interval) should be calculated form the date of the last administered dose of platinum therapy to the date of documentation of progression. – Subjects should have received or refused a PARP inhibitor for BRCA mutant ovarian cancer if indicated. d. Esophageal, Esophagogastric Junction (EGJ), or Gastric Carcinoma – Histologically or cytologically confirmed esophageal (squamous or adenocarcinoma), EGJ, or gastric carcinoma with metastatic or unresectable locally advanced disease – Prior therapy requirements: – Subjects must have received a fluoropyrimidine (fluorouracil or capecitabine) and/or platinum regimen. – Subjects whose tumors are known to be HER2 positive must have failed (progressive disease or unacceptable toxicity) or refused trastuzumab. – Subjects may have received no more than three prior systemic regimens which may include investigational therapies. e. NSCLC – Histologically or cytologically confirmed advanced NSCLC (squamous cell, adenocarcinoma, adenosquamous, or large cell carcinoma) with metastatic or unresectable locally advanced disease – Prior therapy requirements: – Subjects whose tumor is known to have EGFR mutations or ALK gene rearrangements must have received a prior EGFR or ALK inhibitor, respectively. – Subjects whose tumor is known to have a *ROS1* rearrangement or BRAF V600E mutation must have received a *ROS1* or *BRAF* inhibitor, respectively – Subjects must have received or refused anti-PD-1/L1 monotherapy or combination therapy with chemotherapy. – Subjects who have not received an anti-PD-1/L1 therapy as first-line therapy for metastatic disease, must have received or refused anti-PD-1/L1 therapy as second line therapy

	– Subjects may have received no more than three prior systemic regimens which may include investigational therapies. Targeted therapies for EGFR/BRAF V600E mutations or ALK/ROS1 rearrangements are not considered part of these three systemic regimens. f. Head and Neck Carcinoma – Histologically or cytologically confirmed head and neck carcinoma with metastatic or unresectable locally advanced disease – Prior treatment requirements: – Subjects must have received or refused a platinum containing chemotherapy regimen for treatment of primary tumor in adjuvant, locally advanced, or metastatic settings. – Subjects may have received no more than three prior systemic regimens which may include investigational therapies. g. Synovial Sarcoma and Myxoid Liposarcoma/Myoxid Round Cell Liposarcoma – Histologically or cytologically synovial sarcoma or high grade myxoid liposarcoma / myxoid round cell liposarcoma with metastatic or unresectable locally advanced disease – Prior treatment requirements: – Subjects must have previously received either an anthracycline or ifosfamide containing regimen. – Subjects who are intolerant to both anthracycline and ifosfamide must have previously received at least one systemic therapy – Subjects may have received no more than three prior systemic regimens which may include investigational therapies 8. HLA-A*02 positive. 9. Tumor (either an archival specimen or a fresh biopsy) shows MAGE-A4 expression defined as ≥30% of tumor cells that are ≥2+ by immunohistochemistry. All samples must have been pathologically reviewed by an Adaptimmune designated central laboratory confirming expression. 10. Subject has an Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1. 11. Left ventricular ejection fraction (LVEF) ≥50% or the institutional lower limit of normal range, whichever is lower. 12. Fit for leukapheresis and adequate venous access can be established for the cell collection.

	13. Female subject of childbearing potential (FCBP) must have a negative urine or serum pregnancy test AND must agree to use an effective method of contraception starting at the first dose of chemotherapy and continue for at least 12 months or 4 months after the gene modified cells are no longer detected in the blood, whichever is longer. - OR - Male subjects must be surgically sterile or must agree to use a double barrier contraception method or abstain from heterosexual activity with a FCBP starting at the first dose of chemotherapy and continuing for 4 months thereafter (or longer if indicated in the country specific monograph/label for cyclophosphamide). 14. Subject must have adequate organ function as indicated by the laboratory values in the table below:

	<table><tr><th>System</th><th>Laboratory Value</th></tr><tr><td>Hematological</td><td></td></tr><tr><td>Absolute neutrophil count (ANC)</td><td>≥ 1 × 10^9/L (without G-CSF support)</td></tr><tr><td>Platelets</td><td>≥ 75 × 10^9/L (without transfusion support within 7 days prior to leukapheresis and lymphodepletion)</td></tr><tr><td>Hemoglobin</td><td>≥ 80 g/L (without transfusion support within 7 days prior to leukapheresis and lymphodepletion)</td></tr><tr><td>Coagulation</td><td></td></tr><tr><td>Prothrombin time or INR</td><td>≤ 1.5 × upper limit of normal (ULN) unless receiving therapeutic anticoagulation.</td></tr><tr><td>Partial thromboplastin time (PTT)</td><td>≤ 1.5 × upper limit of normal (ULN) unless receiving therapeutic anticoagulation.</td></tr><tr><td>Renal</td><td></td></tr><tr><td>Glomerular filtration rate (estimated or calculated)[1]</td><td>≥ 40 mL/min</td></tr><tr><td>Hepatic</td><td></td></tr><tr><td>Serum total bilirubin</td><td>≤ 1.5 × ULN (unless subject has documented Gilbert's Syndrome with direct bilirubin <35% of total bilirubin)</td></tr><tr><td>Alanine aminotransferase (ALT) /serum glutamic pyruvic transaminase (SGPT)</td><td>≤ 2.5 × ULN</td></tr></table> [1] Renal function (GFR) will be estimated or measured according to standard practice at the treating institution. Renal function will be reassessed at Baseline using the same methodology
Exclusion Criteria	1. HLA-A genotype (The Sponsor will review the results of HLA typing for inclusion and exclusion alleles and will adjudicate subject eligibility based on HLA results): • HLA-A*02:05 positive in either allele. • No HLA-A*02 allele other than A*02:07 or any A*02 null allele (designated with an "N" suffix, e.g. A*02:32N) 2. Subject has received or plans to receive the following therapy/treatment prior to leukapheresis or lymphodepleting chemotherapy, unless stopped according to the wash-out requirements:

Treatment/Therapy	Required Wash-out Prior to Leukapheresis	Required Wash-out Prior to Lymphodepletion
Cytotoxic chemotherapy	3 weeks	3 weeks
Small molecules/tyrosine kinase inhibitor (TKI) such as dabrafenib, trametinib, vemurafanib and cobimetinib. NOTE: No washout period is required for compounds that do not cause bone marrow suppression/lymphopenia or for EGFR and ALK/ROS-1 inhibitors	1 week	1 week
Immune therapy (including monoclonal antibody therapy, checkpoint inhibitors, biologics)	2 weeks	2 weeks
Experimental anticancer vaccine	N/A	2 months in the absence of tumor response. The subject should be excluded if their disease is responding to an experimental vaccine given within 6 months
Gene therapy using an integrating vector	Any use of previous gene therapy using an integrating vector is not permitted	Any use of previous gene therapy using an integrating vector is not permitted
Corticosteroids or any other immunosuppressive therapy. NOTE: Use of topical or inhaled steroids is not an exclusion. See Section 6.6.1 for exceptions.	2 weeks	2 weeks
Investigational treatment	2 weeks or 5 half-lives, whichever is shorter	2 weeks or 5 half-lives, whichever is shorter
Radiation to vital organs (e.g. liver, kidney)	N/A	4 weeks
Radiation to the pelvis	4 weeks	4 weeks
Whole brain radiotherapy (WBRT) or brain stereotactic radiosurgery (SRS)	N/A	2 weeks
Radiotherapy to the target lesions	N/A	A lesion with progression post-radiotherapy may be considered a target lesion. (NOTE: there is no washout period for palliative radiation to non-target organs).
NOTE: Duration of any other anticancer therapies must be discussed with the Sponsor Study Physician		

	3. Toxicity from previous anticancer therapy must have recovered to ≤ Grade 1 or baseline prior to enrollment (except for non-clinically significant toxicities, e.g., alopecia, vitiligo). Subjects with Grade 2 toxicities that are deemed stable or irreversible (e.g., peripheral neuropathy) can be enrolled. 4. History of allergic reactions attributed to compounds of similar chemical or biologic composition to fludarabine, cyclophosphamide or other agents used in the study. 5. History of autoimmune or immune mediated disease. Subjects with hypothyroidism, diabetes, adrenal insufficiency or pituitary insufficiency that are stable on replacement therapy are eligible. Subjects with disorders such as asthma, psoriasis or atopic dermatitis that are well controlled without requiring systemic immunosuppression are also eligible. 6. Subject had major surgery within 4 weeks prior to lymphodepletion; subjects should have been fully recovered from any surgical related toxicities. 7. Leptomeningeal disease, carcinomatous meningitis or symptomatic CNS metastases. Subjects with a prior history of symptomatic CNS metastases must have received treatment (i.e., stereotactic radiosurgery[SRS], whole brain radiation [WBRT] or surgery) and be neurologically stable for at least 1 month, not requiring anti-seizure medications and off steroids for at least 14 days prior to leukapheresis and lymphodepletion. Subjects who have asymptomatic CNS metastases without associated edema, shift, requirement for steroids or anti-seizure medications are eligible. If such a subject receives SRS or WBRT, a minimum period of 2 weeks needs to lapse between the therapy and lymphodepletion. Prophylactic anti-seizure medication is allowed. 8. Other prior malignancy that is not considered by the Investigator to be in complete remission. Resectable squamous or basal cell carcinoma of the skin is acceptable. 9. Electrocardiogram (ECG) showing clinically significant abnormality at Screening 10. Uncontrolled intercurrent illness including, but not limited to: • Ongoing or active infection; • Clinically significant cardiac disease defined by congestive heart failure New York Heart Association (NYHA) Class 3 or Class 4; • Uncontrolled clinically significant arrhythmia; • Acute Coronary Syndrome (ACS) (angina or MI) in last 6 months;

<table>
<tr><td></td><td>

Clinically significant pulmonary disease with pulmonary function with parameters <60% predicted (FEV1 and DLCO) assessed prior to leukapheresis or with a requirement for home oxygen
Interstitial lung disease (pneumonitis), history of pneumonectomy, or of COPD with ≥ one exacerbation within 1 year prior to the Screening visit that required treatment with systemic corticosteroids or resulted in hospitalization.

11. Active infection with human immunodeficiency virus (HIV), hepatitis B virus, hepatitis C virus (HCV), or human T cell leukemia virus (HTLV) as defined below:

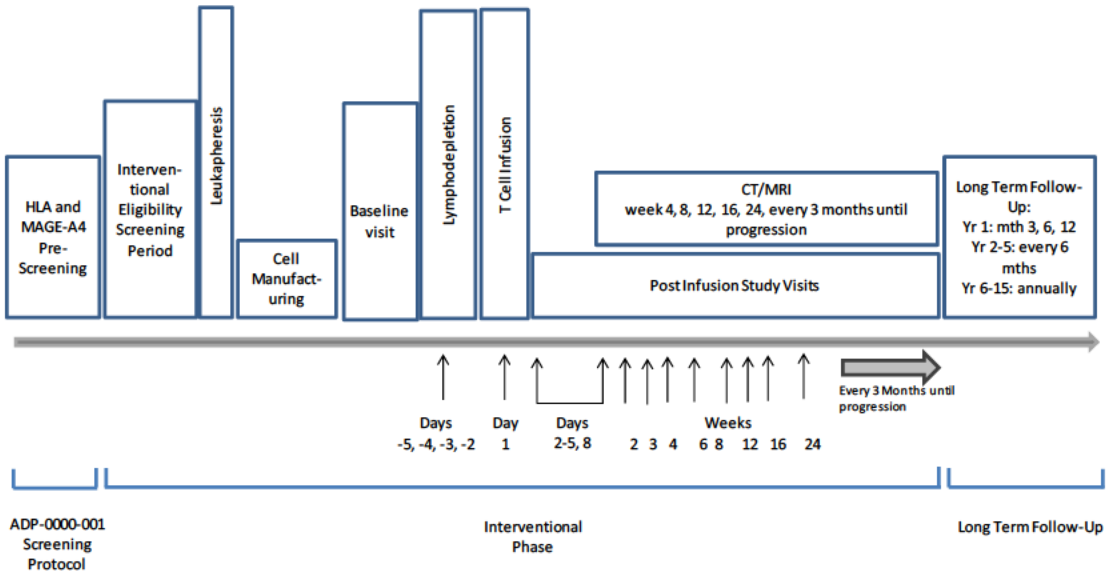
Positive serology for HIV
Active hepatitis B infection as demonstrated by test for hepatitis B surface antigen. Subjects who are hepatitis B surface antigen negative but are hepatitis B core antibody positive must have undetectable hepatitis B DNA and receive prophylaxis against viral reactivation. Prophylaxis should be initiated prior to lymphodepleting therapy and continued for 6 months
Active hepatitis C infection as demonstrated by hepatitis C RNA test. Subjects who are HCV antibody positive will be screened for HCV RNA by any RT PCR or bDNA assay. If HCV antibody is positive, eligibility will be determined based on a negative screening RNA value
Positive serology for HTLV 1 or 2
Re-screening for infectious disease markers is not required at baseline (prior to lymphodepletion) unless > 6 months has elapsed.

12. Pregnant or breastfeeding.
13. In the opinion of the Investigator, the subject is unlikely to fully comply with protocol requirements.
</td></tr>
<tr><td>Investigational Product, Dose, Route, Regimen</td><td>
ADP-A2M4CD8 is the specific peptide enhanced affinity receptor (SPEAR™) TCR product administered by intravenous infusion (on Day 1) following 4 days of lymphodepleting therapy.
<table>
<tr><th>Group</th><th>No. of Subjects</th><th>Transduced Cells</th><th>Cyclophosphamide and Fludarabine Doses[2]</th><th>Interval for Safety Review</th></tr>
<tr><td>1</td><td>3 to 6</td><td>0.8×10^9 to 1.2×10^9</td><td>Cy: 1800 mg/m^2/d × 2d
Flu: 30mg/ m^2/d × 4d</td><td>Minimum 14-day observation period after first subject prior to the start of lymphodepletion in the second and third subjects [1,2,3]</td></tr>
</table>
</td></tr>
</table>

	2	3 to 6	1.2×10^9 to 3.0×10^9	Cy: 1800 mg/m^2/d × 2d Flu: 30mg/ m^2/d × 4d	Minimum 14-day observation period after first subject prior to the start of lymphodepletion in the second and third subjects [1,2,3]
	3	3 to 6	3.0×10^9 to 6.0×10^9	Cy: 1800 mg/m^2/d × 2d Flu: 30mg/ m^2/d × 4d	Minimum 14-day observation period after first subject prior to the start of lymphodepletion in the second and third subjects [1,2,3]
	Expansion	Up to 30 (including dose escalation)	1.0×10^9 to 10×10^9	Cy: 1800 mg/m^2/d × 2d Flu: 30mg/ m^2/d × 4d	No predetermined observation period
	[1] Mesna should be given per institutional standards or at 20% of cyclophosphamide dose (360 mg/m^2) × 4 doses at pre-infusion, 3, 6 and 9 hours relative to the start of each cyclophosphamide infusion. [2] The pre-conditioning chemotherapy is intended to cause lymphodepletion. However, neutropenia is also common. It is recommended that G-CSF is given daily from Day 3 post ADP-A2M4CD8 infusion until resolution of neutropenia in accordance with ASCO guidelines or institutional standard practice. Long-acting (pegylated) G-CSF may be given instead of short acting G-CSF according to institutional standard practice. If pegylated G-CSF is administered, give one dose on Day 3 post infusion of ADP-A2M4CD8. [3]If there are no DLTs observed 14 days after the first subject is dosed, the second and third subject can begin lymphodepletion. If there are no DLTs for 30 days after the third subject is dosed, the next subject can be dosed at the next cell dose level. If DLTs are observed, the group will be expanded to 6 subjects and 14-day dosing stagger between patients will remain.				
Comparator therapy	None				
Statistical Methodology	Descriptive statistics will be provided for safety, laboratory, disposition and antitumor activity data. Bayesian predictive probabilities will be computed during the Expansion phase and provided as guidance to the SRC. Safety, demographic and disposition data will be summarized by cell dose and dose group across cell dose groups. Continuous data will be summarized using means, medians, standard deviations, and ranges, while categorical data will be summarized using frequency counts and percentages. All AEs will be listed and coded by the Medical Dictionary for Regulatory Activities (MedDRA v21 or higher). The number and percent of subjects reporting any AEs will be tabulated by system organ class and preferred term and categorized by cell dose and across cell dose groups. AEs will be tabulated by severity, relationship to treatment and seriousness. AE data will be summarized during the first infusion, the second infusion, and during the combined first and second infusion treatment period.				

	ORR will be summarized by two-sided 95% Wilson and Clopper Pearson confidence intervals (CI) in each dose group and across dose groups. As data permits, ORR may also be summarized by tumor type. The endpoints BOR, TTR, DoR, DoSD, PFS, and OS will be summarized descriptively. In the Expansion group, time-to-event endpoints will be listed and analyzed using Kaplan-Meier (K-M) methodology to estimate the median, and the 25th and 75th percentiles. Overall survival will be assessed at fixed time points such as 1 year and 2 years. For subjects receiving second infusion, ORR may be summarized (data permitting) using two-sided 95% confidence intervals as described above.

1.2. Study Schema



1.3. Time and Events Tables

1.3.1. Main Time and Events (T&E) Table

Written Informed Consent must be obtained prior to performing any protocol procedures. A Pre-screening Informed Consent Form (ICF) will be signed prior to obtaining a blood sample for human leukocyte antigen (HLA) testing and tumor tissue for antigen testing. The Treatment ICF will be signed prior to all other study procedures. Subject ID for this study is the same as the subject ID in Adaptimmune Screening Protocol ADP-0000-001 (Section 8).

Table 1: Main T&E Table

		Interventional Phase																							
	Screening[1]	Leukapheresis	Baseline	Lymphodepleting Chemotherapy				T-cell Infusion	Post-infusion Assessments														Every 3 Months	Study Withdrawal	Comments
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21			
Visit Window	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	± 1 day					± 3 days				± 7 days				± 1 mon	n/a	
Day			-14 to -6	-5	-4	-3	-2	1	2	3	4	5	8	15	22	29									
Week														2	3	4	6	8	12	16	24			
Informed Consent	X																							Section 10.1.4
Demographics	X																							Section 8.1.1
Inclusion/Exclusion	X		X																					Section 5
Tumor type	X																							Section 5, Section 8.1.2
Document tumor-specific mutations	X																							Section 8.1.2
Disease history	X																							Section 8.1.2
Safety and Efficacy Assessments																								
Medical history	X																							Section 8.4.1
Physical exam	X		X					X					X	X										Section 8.4.2

		Interventional Phase																							
	Screening[1]	**Leukapheresis**	**Baseline**	**Lymphodepleting Chemotherapy**				**T-cell Infusion**	**Post-infusion Assessments**														**Every 3 Months**	**Study Withdrawal**	**Comments**
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**			
Visit Window	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	± 1 day					± 3 days				± 7 days				± 1 mon	n/a	
Day			**-14 to -6**	**-5**	**-4**	**-3**	**-2**	**1**	**2**	**3**	**4**	**5**	**8**	**15**	**22**	**29**									
Week														**2**	**3**	**4**	**6**	**8**	**12**	**16**	**24**			
Prior anticancer therapies	X	X	X																					Section 8.4.3
Prior and concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Section 8.4.4
ECOG	X		X										X	X	X	X	X	X	X	X	X	X	X	Section 8.4.5
Height			X																					Section 8.4.7
Weight	X		X													X		X	X	X	X		X	Section 8.4.7
Vital signs	X		X					X[2]	X	X	X	X	X	X									X	Section 8.4.6
ECG	X		X																					Section 8.4.8.1
ECHO/MUGA	X																							Section 8.4.8.2
CT/MRI	X		X													X[9]		X	X	X	X	X	X	Section 8.3.1
Brain MRI			X[4]																					Section 8.4.9
Hematology	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Section 8.4.12 Section 10.2
Lymphocyte subset (CD3, CD4, CD8 if available	X																							Section 8.4.10 Section 10.2
Clinical chemistry	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Section 8.4.13 Section 10.2
Coagulation	X		X																					Section 8.4.14 Section 10.2
Renal function	X		X																					Section 8.4.11

	Interventional Phase																						
	Screening[1]	**Leukapheresis**	**Baseline**	**Lymphodepleting Chemotherapy**				**T-cell Infusion**	**Post-infusion Assessments**												**Every 3 Months**	**Study Withdrawal**	**Comments**
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**			
Visit Window	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	± 1 day					± 3 days				± 7 days				± 1 mon	n/a	
Day			**-14 to -6**	**-5**	**-4**	**-3**	**-2**	**1**	**2**	**3**	**4**	**5**	**8**	**15**	**22**	**29**									
Week														**2**	**3**	**4**	**6**	**8**	**12**	**16**	**24**			
Pregnancy test	X		X																					Section 8.4.17
Infectious disease screening	X		X																					Section 8.4.18 Section 10.2
Pulmonary function tests	X																							Section 8.4.8.4
CMV PCR			X[5]					X[5]						X[5]		X[5]	X[5]	X[5]						Section 8.4.19
Thyroid function tests			X																					Section 8.4.15
C-reactive protein[6]			X					X			X		X	X		X								Section 8.4.20
Ferritin[6]			X					X			X		X	X		X								Section 8.4.20
CARTOX-10								X	X	X	X	X	X											Section 8.4.21
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Section 8.5
Persistence (vector copies)			X						X		X		X	X		X		X	X		X	X		Section 8.4.22 LTFU Table 2
RCL (VSV-G DNA)			X																X		X	LTFU Table 2		Section 8.4.23 LTFU Table 2
Leukapheresis, Lymphodepleting Chemotherapy and Investigational Product Administration																								
Leukapheresis		X																						Section 6.1
Fludarabine				X	X	X	X																	Section 6.2
Cyclophosphamide						X	X																	Section 6.2
ADP-A2M4CD8 infusion								X																Section 6.3
Biomarker Assessments																								
Tumor biopsy			X													X[7]							X	Section 8.6.1

		Interventional Phase																							
	Screening[1]	Leukapheresis	Baseline	Lymphodepleting Chemotherapy				T-cell Infusion	Post-infusion Assessments														Every 3 Months	Study Withdrawal	Comments
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21			
Visit Window	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	± 1 day					± 3 days				± 7 days					± 1 mon	n/a	
Day			-14 to -6	-5	-4	-3	-2	1	2	3	4	5	8	15	22	29									
Week														2	3	4	6	8	12	16	24			
Cytokine and soluble protein analyses[6]			X					X[8]	X		X		X	X		X		X	X		X	X		Section 8.6.2
Liquid biopsy (blood plasma)			X					X[3]					X			X[7]			X		X		X	Section 8.6.3
Cell phenotyping and functional assays			X					X[3]					X	X		X		X	X		X	X	X	Section 8.6.4
Fluid (ascites/pleural)			X (if fluid develops)																						Section 8.6.1

[1] Screening Visit 2 assessments should be completed within 28 days of leukapheresis; CT/ MRI scans and ECHO/MUGA scans performed as standard of care within 4 weeks prior to Screening Visit 2 (prior to study consent) are acceptable.
[2] Measured pre-infusion, and at 5, 15, and 30 minutes, and 1, 1.5, 2, and 4 hours after the infusion has started
[3] Pre-infusion
[4] Within 4 weeks of lymphodepletion
[5] Required at Baseline, Day 1, Week 2, 4, 6, 8 only if seropositive at Screening
[6] If CRS is suspected, CRP and ferritin should be measured approximately every other day until symptoms are improving or an alternative diagnosis is confirmed. Serum cytokines should be collected and submitted.
[7] Can be taken anytime between Week 3 and Week 8 (tumor biopsy and liquid biopsy should be collected at the same visit within 24 hours of each other)
[8] Day 1 cytokine samples to be collected pre-infusion and again 2 to 4 hours post-infusion
[9] The Week 4 scan may occur within +3 days but not before Week 4. Confirmatory scans for clinical response (CR and PR) must be ≥4 weeks from the prior scan.

1.3.2. Long-Term Follow-Up Time and Events Table

Table 2: T&E for Long Term Follow Up

	Time Post-infusion													
			Year 1		Year 2		Year 3		Year 4		Year 5		Years 6-15	Comments
Months	**2**	**3**	**6**	**12**	**18**	**24**	**30**	**36**	**42**	**48**	**54**	**60**	**Annually**	
Visit window	± 1 week	± 1 week	± 2 weeks	± 3 months									± 6 months	
Safety Assessments														
Medical history and physical exam	X	X	X	X	X	X	X	X	X	X	X	X	X	Section 8.4.1 Section 8.4.2
Mutagenic agents, other investigational agents or anticancer therapies	X	X	X	X	X	X	X	X	X	X	X	X	X	Section 8.4.3 Section 8.4.4
Adverse events	X													Section 8.5.1
LTFU adverse events		X	X	X	X	X	X	X	X	X	X	X	X	Section 8.5.8
Hematology	X	X	X	X		X		X		X		X	X	Section 8.4.12 Section 10.2
Clinical chemistry	X	X	X	X		X		X		X		X	X	Section 8.4.13 Section 10.2
Central Lab														
VSV-G DNA (RCL) for safety		X	X	X		X		X		X		X	X	Section 8.4.23 Section 10.6.2
Vector copies (persistence) for safety		X	X	X	X	X	X	X	X	X	X	X	X	Section 8.4.22 Section 10.6.2

2. INTRODUCTION

2.1. Background and Study Rationale

2.1.1. Rationale for Targeting MAGE-A4

Cancer-testis antigens (CTA) comprise of a number of genes that have restricted expression to the testis but have been identified by their expression in various tumor types [Caballero, 2009]. These include NY-ESO-1, MAGE-A family, SSX2, BAGE, GAGE, and CT7 among others. Most of these testis-specific genes are coded on the X chromosome. It should be noted that several of these antigens, including MAGE-A3, MAGE-A10, and MAGE-A8, also have expression in placenta [Caballero, 2009]. In general, melanoma, ovarian cancer, and lung cancer, particularly of the squamous cell type, have the highest frequency of RNA expression across the CTAs. Epithelial cancers such as breast, bladder and prostate cancer have intermediate expression, with frequency of mRNA expression in the range of 30% to 50%. CTAs often have coordinated expression, with several expressed in a single tumor [Gure, 2005]. In addition to RNA, immunohistochemistry (IHC) is often used to determine the expression levels of CTAs. While it is generally seen that mRNA expression of these antigens correlates well with protein expression it should be noted that there is frequently heterogeneous expression of protein across the tumor, with strong expression in a small subset of tumor cells. Epigenetic and post-transcriptional modifications determine protein expression levels under certain conditions.

The function of the CTA in germline tissues or in tumors is generally not well understood. A number of MAGE-A proteins do have functions that may enhance tumor growth. For example, MAGE-A1 proteins may have a role in suppressing differentiation during spermatogenesis and a similar role in inhibiting cell differentiation may be a mechanism by which it promotes tumorigenesis [Laduron, 2004;Simpson, 2005]. There is also evidence that members of the MAGE-A family modulate key transcription factors such as SKIP, p300, p160 (TIF2)/androgen receptor ER-α, and the p53 tumor suppressor [Marcar, 2015]. MAGE-A4 appears to promote cell growth of epithelial cells by preventing cell cycle arrest and inhibiting apoptosis. In one study, overexpression of MAGE-A4 was shown to repress p53 targets, such as BAX and CDKN1A [Bhan, 2012]. In a yeast-two hybrid study, MAGE-A4 was identified as a binding partner for the oncogene gankyrin [Nagao, 2003]. Through these pathways, MAGE expression may protect cells from apoptosis and contribute to the development of tumors by promoting survival [Yang, 2007].

Some CTAs, such as NY-ESO-1, SSX, MAGE-A1, MAGE-A3, and MAGE-A10, have been shown to elicit humoral or cell mediated immune responses [Daudi, 2014]. The approach used here redirects T cells to effectively target tumors by the transduction of antigen-specific enhanced-affinity TCR.

The CTA MAGE-A4 has restricted expression in normal tissue and is expressed to varying frequencies in the following cancers: urothelial (bladder) cancer, melanoma, head and neck cancer, ovarian cancer, non-small cell lung cancer (NSCLC), esophageal cancer, gastric cancer, synovial sarcoma and myxoid/round cell liposarcoma (MRCLS) and have therefore been selected for this Phase 1 dose escalation study.

2.1.2. Rationale for Using ADP-A2M4CD8

Adoptive T cell therapy (ACT) is a treatment that uses a cancer subject's own T lymphocytes with antitumor activity, expanded *in vitro* and re-infused into the subject. The ultimate objective of the process is the stimulation and expansion of potent and antigen-specific T cell immunity. There are numerous recent publications and reviews of adoptive T cell therapy [Kalos, 2013; Klebanoff, 2016; Maus, 2014; Morgan, 2010; Rosenberg, 2008].

Antitumor activity in ''native'' T cells may not be sufficient to induce tumor cell death in most patients with advanced malignancy. Gene-transfer-based strategies have therefore been developed to overcome the consequences of immune tolerance on the tumor-specific T cell repertoire. These approaches provide the potential to redirect T cells to effectively target tumors by the transfer of antigen-specific affinity-optimized T cell receptors (TCRs).

The majority of clinical approaches have employed T cells engineered to stably express transgenes via virus-based transduction. Virus-mediated gene transfer approaches typically employ vectors that are derived from gamma retroviruses or more recently lentiviruses.

MAGE-A4 is a CTA that has restricted expression in normal tissue and is expressed across a range of solid tumors at varying frequencies. ADP-A2M4CD8 specific peptide enhanced affinity receptor (SPEAR™) T cells are genetically engineered to target the subject's MAGE-A4 positive tumor in the context of the appropriate human leukocyte antigen (HLA) expression. ADP-A2M4CD8 are autologous CD4 and CD8 positive T cells that have been transduced with a self-inactivating lentiviral vector expressing a high affinity MAGE-A4 specific T cell receptor (TCR) and an additional CD8α co-receptor. The affinity enhanced ADP-A2M4 TCR targets the tumor antigen MAGE-A4 and activates engineered T cells. It recognizes the MAGE-A4$_{230-239}$ (GVYDGREHTV) peptide sequence derived from MAGE-A4, when presented in the HLA-A*02-GVYDGREHTV antigen complex. This TCR is presently being explored in Adaptimmune's Protocol "Phase 1 Dose Escalation, Multi-tumor Study to Assess the Safety, Tolerability and Antitumor Activity of Genetically Engineered MAGE-A4^{c1032}T in HLA-A2+ Subjects With MAGE-A4 Positive Tumors (NCT03132922) [Hong, 2018]. The CD8α co-receptor, (unique to ADP-A2M4CD8), is designed to provide additional functionality to CD4 T cells. Because CD4+ T cells have a weak effector function in response to Class I antigens, a CD8α co-receptor was introduced in ADP-A2M4CD8 alongside the TCR, in order to increase TCR binding avidity and enhance the polyfunctional response of engineered CD4+ T cells against MAGE-A4 positive tumor.

2.1.3. Discovery of ADP-A2M4 TCR and CD8α Enhancement

Several peptides derived from MAGE proteins have been identified by mass spectroscopy from tumor cell lines, including the HLA-A*02-restricted peptide MAGE-A4$_{230-239}$ (GVYDGREHTV). HLA Class I molecules are involved in the presentation of antigenic peptides on tumors to T lymphocytes. The prevalence of HLA subtypes varies from population to population, the most common in the western world being HLA-A2. Among the HLA-A2 allelic variants, the most prevalent are HLA-A*02:01 (approximately 45% of Caucasian and Hispanic populations) and HLA-A*02:06 (www.allelefrequencies.net). Adaptimmune generated 20 parental TCRs that recognize the HLA-A*02-restricted MAGE-A4 peptide GVYDGREHTV.

From these, one demonstrated some response toward natively MAGE-B2 and MAGE-A4 positive cell lines and was selected for engineering. From three strongly MAGE-A4 specific TCRs, cellular testing for potency and specificity identified ADB1032 as being the optimal candidate to move forward. ADB1032 demonstrated enhanced potency against MAGE-A4 positive tumor cell lines, while retaining a favorable specificity and safety profile. ADP-A2M4 is currently being investigated for safety and efficacy under IND 17235 (ADP-0044-001).

In ADP-A2M4CD8, a wild-type CD8α co-receptor was introduced alongside the ADP-A2M4 TCR in order to enhance engineered CD4+ T polyfunctional responses against tumor antigens. ADP-A2M4CD8 is designed to improve upon the Investigational Product, ADP-A2M4. It is comprised of autologous CD4 and CD8 T cells which will be obtained from eligible subjects who have MAGE-A4 expressing tumors and are HLA-A*02 positive.

The addition of a CD8α co-receptor directly impacts TCR binding to the HLA-peptide complex in CD4+ T cells, enhancing CD4+ T cell effector function. ADP-A2M4CD8 cells do not display any new cross-reactivity and transduced T cells do not display additional alloreactivity *in vitro*. As expected, alloreactivity from both ADP-A2M4 and ADP-A2M4CD8 was only seen towards two HLA-A*02:05 positive cell lines. Therefore, patients who are HLA-A*02:05 positive will be excluded from the study. Patients with either HLA-A*02:07 or any A*02 null allele as the sole HLA-A*02 allele will be also excluded due to decreased activity with these alleles. No additional alloreactivity was noted, and importantly, no targets induced an enhanced alloreactive response from ADP-A2M4CD8 cells. Together, these data demonstrate that addition of the CD8α co-receptor does not alter the specificity of the ADP-A2M4 TCR. Details regarding design and preclinical testing of ADP-A2M4CD8 are provided in the Investigators Brochure.

In preclinical *in vitro* assays, ADP-A2M4CD8 showed a clear improvement in T cell activation (when cultured with antigen positive cells), as measured by increased CD40L surface expression, particularly in the CD4+ fraction. When an additional arm of the immune system, dendritic cells (DCs), was introduced in co-cultures, a marked improvement was seen with the second generation ADP-A2M4CD8. Cytokines release from both DCs (IL-12, MIG) and T cells (IFNy, IL-2 and other Th1) was improved compared to cultures containing the first generation ADP-A2M4 cells. Additionally, a conversion of CD4+ T cells was seen, from being unable to kill MAGE-A4 positive 3D microspheres, to having an effective cytotoxic function when transduced with ADP-A2M4CD8. Therefore, CD4+ T cells transduced with ADP-A2M4CD8 display not only CD4+ helper functions, but also improved T cell effector functions.

2.1.4. Current Therapies for Tumors Expressing MAGE-A4

There is an unmet need for patients with advanced disease who have progressed after first line therapy. Subjects with advanced (metastatic or inoperable) disease and whose tumors express MAGE-A4 will be included in this study, which is designed to investigate if ADP-A2M4CD8 can yield a clinically meaningful response rate in this subject population.

MAGE-A4 is expressed to varying frequencies in the following cancers: urothelial (bladder) cancer, melanoma, head and neck cancer, ovarian cancer, non-small cell lung cancer (NSCLC), esophageal cancer, gastric cancer, synovial sarcoma, and myxoid/round cell liposarcoma (MRCLS) and have therefore been selected for this Phase 1 dose escalation study. Four of these

cancers are associated with environmental carcinogens or pathogens (e.g., sun exposure, smoking, human papilloma virus [HPV]), have a high nonsynonymous mutation burden, and are responsive to immunotherapeutic modalities (NSCLC, urothelial, melanoma, head and neck). Although the overall tumor mutational burden has been associated with improved efficacy of immunotherapy, it remains unclear how specific mutational properties are associated with neoantigen presentation and response to immunotherapy. The current and emerging treatment options are briefly summarized (not meant to be a comprehensive overview) in the subsections below. The overall response rate (ORR) in second line therapy and beyond for the populations proposed in this study ranges from 10 to 30%. Despite the rapid development of promising targeted therapies for these cancer types, there is still an unmet need for patients who do not respond to or progress after currently approved therapies.

Urothelial Cancer

In the US, the incidence and mortality of urothelial cancer are approximately 77,000 and 16,000 cases annually respectively. Ninety percent of urothelial cancers originate in the bladder, while 8% originate in the renal pelvis and 2% in the ureter or urethra.

The average survival for metastatic urothelial bladder cancer (mUBC) is 12 to 15 months. Combination chemotherapy regimens are the primary treatment for metastatic bladder cancer: commonly used regimens are gemcitabine with cisplatin or carboplatin or MVAC (methotrexate, vinblastine, Adriamycin, cisplatin) [Loehrer, 1992; Saxman, 1997].

The FDA approved several PD-1/PDL-1 inhibitors for the treatment of patients with locally advanced or metastatic urothelial carcinoma including pembrolizumab, atezolizumab and nivolumab.

Melanoma

In the US, the 2018 incidence and mortality rates of melanoma of the skin are estimated to be approximately 99,550 and 13,460 respectively (Cancer facts and figures 2016). Treatment for melanoma has changed dramatically in the last decade with advances in both targeted therapy and immunotherapy.

Ipilimumab [Hodi, 2010], nivolumab [Weber, 2015], and pembrolizumab [Ribas, 2015] are approved for the treatment of patients with metastatic melanoma and have shown progression-free survival (PFS) and ORR benefits.

About half of all melanomas harbor an activating mutation in the BRAF gene. BRAF inhibitors, vemurafenib and dabrafenib were each approved initially as monotherapies for the treatment of patients with BRAFv600E mutation positive metastatic melanoma based on the results of randomized trials against dacarbazine [Chapman, 2011; Hauschild, 2012]. Improved efficacy was subsequently demonstrated with the combination of a BRAF inhibitor with a MEK inhibitor and has shown a significant overall survival (OS) benefit in previously untreated patients with metastatic melanoma with *BRAF* V600E or V600K mutations, as compared with dabrafenib monotherapy [Robert, 2015]. The combination has also shown improvement in DFS in the adjuvant setting for high-risk resectable melanoma. Similarly, the combination of vemurafenib and cobimetinib demonstrated an improvement in OS compared to vemurafenib monotherapy [Wongchenko, 2015].

Head and Neck Cancer

Head and neck cancer arises in the epithelium of the paranasal sinuses, nasopharynx, oropharynx, oral cavity, hypopharynx and larynx. Risk factors include the use of tobacco and alcohol, as well as viral infections, namely human papillomavirus (HPV) infection (primarily in oropharyngeal cancers), and Epstein-Barr virus (EBV) infection (in nasopharyngeal cancers).

The majority of patients with head and neck cancer present with locally advanced disease. Those who present with early Stage I or II disease are often treated with either radiation or surgery and have excellent prognosis. For those patients with Stage III or IV locally advanced squamous cell carcinoma of the head and neck (SCCHN), the relapse and 3-year survival rates following surgery and/or radiotherapy (RT) with or without chemotherapy are 40% to 60% and 30% to 50% respectively [Posner, 2007]. Bolus cisplatin every three weeks during radiation is often used in patients with advanced disease [Bernier, 2004; Cooper, 2004].

5-Fluoruracil (5-FU)/cisplatin was the standard induction regimen until the approval of the addition of docetaxel to 5-FU/cisplatin in locally advanced head and neck tumors. Median PFS and OS were significantly longer in the docetaxel/5-FU/cisplatin arm [Vermorken, 2007]. Cetuximab is approved in combination with radiation in previously untreated patients [Bonner, 2006], in combination with platinum and 5-FU for recurrent or metastatic disease in first line [Vermorken, 2008], or as monotherapy after failure of cisplatin.

In 2016 FDA approved both pembrolizumab and nivolumab for the treatment of patients with recurrent or metastatic SCCHN with disease progression on or after platinum-containing chemotherapy.

Ovarian Cancer

Ovarian, fallopian tube, and primary peritoneal cancer have a common derivation from the Müllerian epithelium; they generally follow a similar clinical course with a pattern of peritoneal spread and are treated following similar approaches. In 2018, the incidence and mortality of these cancers in the US are expected to be approximately 22,040 and 14,070 cases, respectively [Pennington, 2012].

Most patients present with advanced disease, including nodal and intraperitoneal involvement, particularly in the case of high-grade serous carcinomas. Radical hysterectomy, bilateral oophorectomy and optimal cytoreduction are the goals of the initial surgical treatment. Following resection, patients with advanced or metastatic disease generally receive treatment with platinum and taxanes as first line chemotherapy.

Approximately 80% of patients relapse after first-line platinum and taxane-based chemotherapy. Patients whose tumors recur after 6 months following completion of platinum-based chemotherapy are generally treated with additional platinum-based therapy. Patients who progress during treatment or within 6 months of treatment cessation are thought to have platinum refractory or resistant disease and are generally not candidates for further platinum-based therapies. Several chemotherapeutic agents such as paclitaxel, topotecan and pegylated liposomal doxorubicin are given alone or in combination with bevacizumab for recurrent disease. Finally, PARP inhibitors, olaparib and rucaparib, are approved as single agents for patients with BRCA mutations who have been treated with several prior lines of chemotherapies (LYNPARZA®

2018; RUBRACA® 2018). In addition, olaparib and niraparib have been approved in the US as maintenance therapy for women with recurrent disease who have achieved a complete response (CR) or partial response (PR) to platinum-based therapy (LYNPARZA®, 2018; ZEJULA®, 2019).

Non-Small Cell Lung Cancer (NSCLC)

Lung cancer is the third most common form of the disease in the US after prostate cancer in men and breast cancer in women. It is estimated that approximately 234,030 new cases will be diagnosed in 2018 accounting for about 13% of all cancer diagnoses [Cancer Facts and Figures, 2016].

NSCLC accounts for 84% of lung cancer and may be classified according to histology as adenocarcinoma (40%), which usually originates in peripheral lung tissue; squamous-cell carcinoma (25%) typically occurring close to large airways; and large cell carcinoma (10%) [NIH, 2016]. Subsets of adenocarcinomas can be further defined at the molecular level by the specific mutations of genes coding, for example, for epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase receptor (ALK).

For early-stage NSCLC, surgery is the treatment of choice, followed by adjuvant chemotherapy. Chemoradiation alone or followed by surgery is commonly used for Stage IIIA NSCLC. For patients with advanced NSCLC (stages IIIB and IV), recommended [NCCN, 2016] first line treatment is with platinum-based doublet chemotherapy. This generally consists of cisplatin or carboplatin with another cytotoxic agent (e.g., pemetrexed, taxanes, gemcitabine). Other agents such as bevacizumab or cetuximab may be added to the regimen. PD-1 inhibition has improved the survival of patients with NSCLC when given in the front-line setting. Pembrolizumab, in combination with pemetrexed and platinum chemotherapy, is approved for the first-line treatment of patients with metastatic nonsquamous NSCLC, with no EGFR or ALK genomic tumor aberrations. Pembrolizumab, in combination with carboplatin and either paclitaxel or nab-paclitaxel, is also approved for the first-line treatment of patients with metastatic squamous NSCLC. Durvalumab is approved in the maintenance setting for patients with unresectable stage III NSCLC whose disease has not progressed following concurrent platinum-based chemotherapy and radiation therapy.

Targeted therapies are the treatment of choice for patients with specific mutations. Erlotinib and afatinib are indicated for patients whose tumors contain sensitizing EGFR mutations, and crizotinib is indicated in patients whose tumors contain ALK or ROS1 rearrangements. Lorlatinib is approved for patients whose disease has progressed on crizotinib and at least one other ALK inhibitor for metastatic disease or whose disease has progressed on alectinib or ceritinib as the first ALK inhibitor therapy for metastatic disease.

Both pembrolizumab and nivolumab have been approved by FDA as monotherapy for patients with disease progression after cisplatin based therapy or after targeted therapy if the tumors contain EGFR or ALK alterations.

Esophageal Cancer, Esophagogastric Junction (EGJ) Cancer, and Gastric Cancer

In Western countries, the incidence of adenocarcinoma of the esophagus and EGJ is rising rapidly, while the incidence of squamous cell carcinoma of the esophagus is declining owing to a

decrease in tobacco use. The estimated combined incidence and mortality of esophageal and gastric cancers in 2018 in the US are 43,710 and 26,650 cases respectively [Cancer Facts and Figures, 2016]. Many patients present with advanced disease, a stage associated with 5-year survival of only 5% to 15% and median survival of 8 to 10 months. The mainstay of treatment for advanced disease is fluoropyrimidine and platinum-based combination chemotherapy. Low response rates and high levels of toxicity are observed with second-line chemotherapy. Trastuzumab prolongs survival in patients with Her2-neu over-expressing gastric cancer (10 to 30% of gastric cancer) in first-line chemotherapy and addition of the anti VEGFR-2 antibody ramucirumab in second line improves OS and PFS when compared to chemotherapy alone [Orditura, 2014]. There is some evidence that esophagogastric cancer can respond to immunotherapy [Kim, 2005; Popiela, 2004; Ralph, 2010], but no other treatments beyond palliative chemotherapy are available for patients with advanced disease. Pembrolizumab was approved in 2017 for patients with recurrent locally advanced or metastatic, gastric or gastroesophageal junction adenocarcinoma whose tumors express PD-L1 as determined by an FDA-approved test.

Synovial Sarcoma and Myxoid/Round Cell Liposarcoma

Sarcomas are rare malignant tumors originating from mesenchymal cells and their precursors, and represent approximately 1% of all cancers in adults worldwide each year (10% of cancers in children, and 8% of cancers in adolescents) and approximately 2% of cancer related mortality [Singer, 2000; Amankwah, 2013]. The estimated international incidence rates of soft tissue sarcoma ranges between 4 and 6 cases per 100,000 per year [Stiller, 2013; Ferrari, 2011]. Soft tissue sarcomas consist of approximately 50 different histological subtypes.

Synovial Sarcoma

Synovial sarcoma represents 5% of all soft tissue sarcoma (STS) and is characterized by the presence of a translocation between SYT on the X chromosome and SSX1, SSX2 or SSX4 on chromosome 18. The disease affects young individuals with a median age in the third decade; with 70% of the diagnoses occurring in subjects under 40 years old.

Surgery is the standard therapy for localized disease. Patients with advanced synovial sarcoma receive ifosfamide and/or doxorubicin, as the first-line of therapy [ESMO, 2014]. Lartruvo (olaratumab) in combination with doxorubicin, was recently granted accelerated approval for the first-line treatment of adults with advanced STS with a histologic subtype for which an anthracycline-containing regimen is appropriate and which is not amenable to curative treatment with radiotherapy or surgery.

There is no specific standard of care in second-line therapies and beyond. Pazopanib is approved in the U.S and in Europe for patients with synovial sarcoma previously treated with chemotherapy [Votrient™ US Prescribing Information, 2015; Votrient™ EU SmPC, 2015]. Additional agents used in second line treatment of synovial sarcoma include high dose ifosfamide and combination therapy with docetaxel and gemcitabine. Effective treatment options for patients with advanced relapsed synovial sarcoma are limited. The median survival upon relapse from first-line therapy is approximately 12 months [Minchom, 2010].

Clinical trials investigating the efficacy and safety of adoptive T cell therapy are ongoing and have demonstrated evidence of clinical efficacy. In an open-label non-randomized multi-cohort pilot study of genetically engineered NY-ESO-1 T cells in HLA-A2^{+} patients with synovial sarcoma (NCT01343043), in the first cohort confirmed responses (1 CR and 5 PR) were observed in 6 of 12 (50%) subjects who received NY-ESO-1^{c259}T. The median duration of response (DOR) was approximately 31 weeks with a range of 13 weeks-72 weeks [D'Angelo, 2017].

Myxoid/Round Cell liposarcoma (MRCLS)

MRCLS is a subtype of liposarcoma that is associated with specific translocations, t(12;16 (q13;p11) or t(12;22) (q13;q12) and represents about 30% to 35% of liposarcomas and 5% to 10% of all adult STS (WHO 2002). MRCLS commonly presents at an age ranging from 35 to 55 years. Myxoid round cell tumors with a round-cell component >5% have a poor prognosis with a 5-year survival rate of approximately 50% to 75% because they recur locally and tend to metastasize quickly and widely [Smith, 1996]. The median time from diagnosis to metastases is 35 months.

Treatment involves the wide surgical excision of the tumor and surrounding tissue and high grade round cell liposarcoma may be treated with pre-operative chemotherapy and/or pre-operative or post-operative radiotherapy [NCCN, 2016].Doxorubicin and ifosfamide are the first line systemic treatment options for patients with metastatic disease. Retrospective analyses in previously untreated patients demonstrated response rates of approximately 38% to 45% [Jones, 2005; Katz, 2012]. Once patients relapse or develop metastatic disease treatment is aimed at slowing that pace of progression. A variety of therapies are used in the second-line setting and beyond although only trabectedin and eribulin are approved. Despite the approval of these two agents, OS in patients with relapsed disease remains 12 to13 months [Demetri, 2016; Schöffski, 2016].

2.2. Benefit/Risk Assessment

The results of non-clinical studies conducted with ADP-A2M4CD8 are summarized in the ADP-A2M4CD8 Investigator's Brochure. This section outlines the potential benefits, risks and the overall benefit/risk assessment for this study.

2.2.1. Benefit

The MAGE-A4 CTA is widely expressed in a variety of solid tumors and not expressed in normal healthy adult tissues. A patient's T cells can be genetically engineered to recognize tumor antigens. The TCR approach to engineered T cell therapy is attractive because TCRs are capable of recognizing not only cell surface proteins (as is the case with chimeric antigen receptors [CARs]) but also any internal protein, since TCRs recognize peptide fragments in the context of HLA. In addition, the TCR approach best mimics the natural function of the T cell by recruiting the endogenous signaling molecules and adhering to correct spatial orientation between the T cell and its target. These aspects may contribute to enhanced safety and activity of TCR engineered cells.

Several clinical trials investigating the efficacy and safety of adoptive T cell therapy with Adaptimmune's TCRs are ongoing. Efficacy has been demonstrated with other adoptive T cell therapies, including NY-ESO-1^{c259}T [Rapoport, 2015; Merchant, 2015; Araujo, 2019; D'Angelo, 2018a; Mackall, 2017].

NY-ESO-1^{c259}T is an enhanced affinity TCR that recognizes NY-ESO-1 tumor antigen and has been administered to subjects with advanced tumors in multiple myeloma, melanoma, soft tissue sarcoma, NSCLC, and ovarian cancer following conditioning chemotherapy.

Efficacy of NY-ESO-1^{c259}T has been demonstrated in Cohort 1 of a multi-cohort study in patients with synovial sarcoma. Subjects were lymphodepleted with fludarabine 30 mg/m^2/day × 4 days; and cyclophosphamide 1800 mg/m^2/day × 2 days. Twelve patients were treated with NY-ESO-1^{c259}T. The ORR was 50% (1 CR; 5PR) and median time to response was 6.2 weeks (range 4 to 9 weeks). The median PFS was 15 weeks (range 8 to 38 weeks) and the median duration of response was 30.9 weeks (range 13 to 72 weeks) [D'Angelo, 2018].

In patients with advanced myeloma, NY-ESO-1^{c259}T has been investigated in the context of melphalan and autologous hematopoietic stem cell transplant. The results on the first 20 multiple myeloma subjects were reported [Rapoport, 2015]. ORR at Day 100 was 76%, and at Year 1, 52% of patients were disease progression free. The median PFS was approximately 13 months (range 3 to 61 months), and the median OS was approximately 35 months (range 6 to 68 months). At study completion, 3 treated patients had remained disease progression-free for 61, 56, and 39 months [Rapoport, 2017]. T cell expansion was detected in all subjects and persistence at Day 100 was observed in all but 1 subject [Rapoport, 2015].

This data suggests that affinity optimized TCRs can be safe and effective and supports the potential therapeutic benefit of TCR therapy in patients with malignancies expressing the relevant antigen.

The benefit of ADP-A2M4CD8 is not known at present, however, the MAGE-A4 antigen is highly expressed in the proposed tumor types and therefore the potential therapeutic benefit of ADP-A2M4CD8 is being investigated in this trial.

2.2.2. Risk

This study is the first in human study with ADP-A2M4CD8. Extensive preclinical evaluation of ADP-A2M4CD8 (ADP-A2M4CD8 Investigator Brochure) support the specificity, safety, and antitumor activity. The addition of a CD8α co-receptor to ADP-A2M4 directly impacts TCR binding to the HLA-peptide complex in CD4+ T cells, enhancing CD4+ T cell effector function. ADP-A2M4CD8 does not display any new cross-reactivity and transduced T cells do not display additional alloreactivity *in vitro.*

The safety and tolerability of ADP-A2M4 is being assessed in a Phase 1 trial of multiple tumor types (ADP-0044-001). It is anticipated that certain toxicities observed with ADP-A2M4 are common to other T cell therapies and would be expected to occur with ADP-A2M4CD8. ADP-A2M4 has demonstrated an AE profile that has been manageable and acceptable within the context of benefit: risk. Most AEs were consistent with those typically experienced by patients with advanced cancer undergoing cytotoxic chemotherapy or cancer immunotherapy. Toxicities such as cytokine release syndrome (CRS), encephalopathy syndrome (ES) and

pancytopenia/aplastic anemia are AEs associated with T-cell therapies [Neelapu, 2018; D'Angelo, 2017]. Furthermore, several investigators have observed that pre-infusion tumor burden, severity of CRS, and T-cell expansion appear to be associated with response [Mueller, 2017; Mueller, 2018].

Guidelines for management of these events are included in protocol Section 10.4. An advantage of TCR therapy is that it is generally administered once, and the vast majority of toxicities resolve within 4 to 6 weeks after T cell infusion.

The study incorporates several measures to address and mitigate the potential risks of treatment with ADP-A2M4CD8, including: (1) exclusion of subjects with HLA-A*02:05 in either allele or with either HLA-A*02:07 or any A*02 null allele (designated with an "N", e.g., A*02:32N) as the sole HLA-A*02 allele based on the preclinical activity and alloreactivity data; (2) use of a validated clinical trial assay with precision and reproducibility for the selection of subjects with MAGE-A4 expression in their tumors; (3) step-wise escalation of the T cell dose; (4) staggered enrollment in the dose escalation groups such that there is a 14-day observation period after T cell infusion of the first subject in each group; (5) treatment in specialized academic centers experienced with the management of toxicities associated with autologous T cell therapies; (6) guidelines for management of toxicities including CRS, ES, and pancytopenia/aplastic anemia as well as preventive measures for infectious complications; (7) real time review of all SAEs through robust routine pharmacovigilance measures; (8) evaluation of safety throughout the study by a Safety Review Committee (SRC) including expertise external to Adaptimmune.

2.2.3. Overall Benefit: Risk Conclusion

Subjects with inoperable, advanced, or metastatic urothelial cancer, melanoma, head and neck cancer, ovarian cancer, NSCLC, esophageal cancer, EGJ, gastric cancer, synovial sarcoma, or MRCLS who have progressed following other therapies, constitute a population with a high unmet medical need. A Phase 1 clinical study with ADP-A2M4 and preclinical studies support the specificity, safety, and antitumor activity of ADP-A2M4CD8 T cells. Patients with advanced disease have limited treatment options and a poor prognosis. Measures to ensure safe administration of ADP-A2M4CD8 have been included in this study protocol, with close monitoring for toxicities and guidelines for their management. The potential risks identified in association with ADP-A2M4CD8 are justified by the anticipated benefits which may be afforded to patients, therefore the benefit: risk for ADP-A2M4CD8 supports initial testing in the clinic in the defined study population.

3. OBJECTIVES AND ENDPOINTS

Objectives	End Points
Primary:	
To evaluate the safety and tolerability of autologous genetically modified T cells (ADP-A2M4CD8) in subjects with HLA-A*02 and MAGE-A4 positive inoperable locally advanced or metastatic tumors	• Incidence of dose-limiting toxicities (DLTs) and determination of optimally tolerated dose range, adverse events (AEs), and serious adverse events (SAEs) • Replication Competent Lentivirus (RCL) • T cell Persistence and Insertional oncogenesis (IO)
Secondary:	
To evaluate the antitumor activity of autologous genetically modified T cells (ADP-A2M4CD8) in HLA-A*02 subjects with MAGE-A4 positive inoperable locally advanced or metastatic tumors	• Overall Response Rate (ORR) based on confirmed responses (CR/PR) by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 • Best overall response (BOR) • Time to response (TTR) • Duration of response (DoR) • Duration of stable disease (DoSD) • Progression free survival (PFS) • Overall survival (OS)
Exploratory:	
[redacted]	

Objectives	End Points
[redacted]	

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 1, dose-escalation, open-label study of genetically engineered ADP-A2M4CD8 in HLA-A*02:01 subjects with MAGE-A4 expressing locally advanced inoperable or metastatic cancer of the following types: urothelial, melanoma, head and neck, ovarian, NSCLC (squamous, adenocarcinoma, adenosquamous, or large cell), esophageal (squamous and adenocarcinoma), EGJ, gastric, synovial sarcoma or MRCLS.

Up to 30 subjects including the subjects in the dose escalation groups will be enrolled to robustly evaluate the clinical benefit:risk in subjects who received the ADP-A2M4CD8 therapy.

Enrollment is expected to continue for approximately 18 months.

4.1.1. Pre-screening

Subjects must be aged ≥18 years and must have a diagnosis of advanced (metastatic or inoperable) urothelial, melanoma, head and neck, ovarian, NSCLC (squamous, adenocarcinoma, adenosquamous, or large cell), esophageal (squamous and adenocarcinoma), EGJ, gastric, synovial sarcoma or MRCLS to be eligible.

Subjects will be screened for the presence of the relevant HLA-A alleles and MAGE-A4 expression on their tumor through the Screening Protocol (ADP-0000-001, NCT02636855).

4.1.2. Screening

Subjects who have been identified as positive for the relevant HLA alleles and MAGE-A4 tumor antigen in the Screening Protocol (ADP-0000-001) will be asked to sign the Treatment Informed Consent Form (ICF) and enter Screening to determine full eligibility for this study.

4.1.3. Enrollment

Subjects who sign the Treatment ICF and meet the protocol defined eligibility criteria (Section 5.2 and Section 5.3) will be enrolled. Subjects who do not meet the protocol defined eligibility criteria are screen failures.

Enrolled subjects will undergo leukapheresis for collection of autologous cells for processing and manufacture into the ADP-A2M4CD8 Investigational Product (IP). Leukapheresis should be performed as soon as possible after the subject is determined to be eligible for study participation.

Anticancer therapy may be administered to subjects between screening and leukapheresis. However, following leukapheresis, a subject must receive ADP-A2M4CD8 as the next therapy. If, in the opinion of the Investigator, the subject requires immediate therapy after leukapheresis, the subject may receive bridging therapy for the period during which the subject is awaiting the manufacture of ADP-A2M4CD8. Following this bridging therapy, the subject must adhere to the mandatory washout periods (Section 5.3) prior to receiving ADP-A2M4CD8. In addition, subjects must continue to have measurable disease following the bridging therapy in order to receive ADP-A2M4CD8.

Prior to the administration of lymphodepleting chemotherapy, all eligibility criteria will be reconfirmed and Baseline tumor assessment obtained.

Once the ADP-A2M4CD8 cells are available at site, subjects will undergo lymphodepleting chemotherapy with fludarabine 30 mg/m^2/day for 4 days (Day -5 through Day -2) and cyclophosphamide 1800 mg/ m^2/day for 2 days (Days -3 and -2) (Section 6.2) followed by infusion of ADP-A2M4CD8 on Day 1 (Section 6.3). The lymphodepleting chemotherapy may be given as an outpatient treatment or subjects may be hospitalized at the discretion of the Investigator.

It is required that the T cell infusion is given as an inpatient procedure and that subjects are hospitalized for 72 hours following dosing. This allows for close monitoring of post-infusion AEs during the dose escalation phase of the study. The subject may be discharged thereafter if medically stable at the discretion of the Investigator. During Expansion, subjects may be hospitalized at the discretion of the Investigator.

Safety, antitumor activity, and biomarker assessments to be conducted at each visit are outlined in the Time and Events tables (Table 1 and Table 2). Antitumor activity will be assessed by the Investigator using RECIST v1.1. To allow time for the immune response to become apparent and for potential transient inflammatory reaction of the disease to the treatment (i.e., “tumor flare”), response will not be assessed before 28 days post infusion of ADP-A2M4CD8. Therefore, imaging scans should not be performed earlier than 28 days post-infusion unless there is a clinical need.

Subjects will continue to have scans for antitumor activity during the Interventional Phase of the study, until disease progression is established. Once progression is established, no further scans will be performed for this study, however, subjects will continue to be followed for observation of delayed AEs (Table 2) in accordance FDA and EMA requirements for gene therapy clinical trials [FDA, 2006a; FDA, 2010; EMA, 2009].

Subjects will be seen in the clinic for evaluation according to Main Time and Events Table (Table 1, Section 1.3.1) until disease progression, death or withdrawal.

Subjects who have a confirmed response following the initial infusion (or clinical benefit ≥4 weeks after the first T-cell infusion) and whose tumor continues to express the MAGE-A4 antigen may be eligible for a second infusion with engineered T-cells, as long as they meet eligibility criteria defined in Section 5.4.

Subjects who end the Interventional Phase of the study will undergo assessments/procedures according to the LTFU Time and Events Table (Table 2, Section 1.3.2). The timepoint at which the subject switches to the LTFU assessments/procedures will be driven by the timepoint at which the subject progresses, e.g., if there is disease progression at Week 12, the next visit would be due at Week 24 (Month 6).

The study will be considered complete once all subjects complete 15 years of follow-up, die or withdraw early from the study.

4.2. Scientific Rationale for Study Design

This Phase 1 study is designed as a cell dose escalation trial in HLA-A*02 subjects with MAGE-A4 positive locally advanced inoperable or metastatic cancer of the following types: urothelial, melanoma, head and neck, ovarian, NSCLC, esophageal, EGJ, gastric, synovial sarcoma, and MRCLS. The study will enroll up to 18 subjects with inoperable or metastatic (advanced) cancers of these types in the dose escalation phase. The study will enroll subjects using a modified 3+3 cell dose escalation design to evaluate Dose Limiting Toxicities (DLT) and determine the target cell dose range. Following the dose escalation phase the study will be expanded to enroll additional subjects (up to a total of 30 subjects in the study) at the dose range shown in Table 4 across all the eligible tumor types to better characterize and assess overall safety and efficacy.

4.2.1. Pre-Screening for HLA Alleles and MAGE-A4 Expression

4.2.1.1. HLA

Subjects must express at least 1 HLA-A allele capable of presenting the MAGE-A4 target peptide, which is any A*02 allele other than HLA-A*02:05, HLA-A*02:07, or any A*02 null allele. For safety reasons, subjects expressing A*02:05 are not eligible, irrespective of the nature of the second A*02 allele.

To ensure that the subject expresses the appropriate HLA-A*02 alleles, HLA testing of a blood sample is required. The blood sample will be screened at a central reference laboratory for HLA expression using an FDA approved HLA Sequencing System for sequence based typing (SBT) of HLA. Subjects will be screened for the presence of the relevant HLA-A alleles through the Screening Protocol (ADP-0000-001).

4.2.1.2. MAGE-A4 Expression in Tumor

High expression of MAGE-A4 has been reported across several cancer indications including, lung, esophageal, head and neck, bladder, ovarian, breast and colorectal cancers [Tajima, 2003; Forghanifard, 2011; Errington, 2012; Barrow, 2006; Alves, 2007; Cuffel, 2011; Kocher, 2002; Daudi, 2014; Otte, 2001; Cabezon, 2013]. More recently, MAGE-A4 expression was reported in synovial sarcoma (82%) and myxoid liposarcoma (68%) cases [Iura, 2017a; Iura, 2017b].

ADP-A2M4 cells have been shown to produce strong IFNγ responses against tumor cell lines (derived from non-small cell lung cancer, prostate carcinoma, melanoma and ovarian carcinoma) expressing high MAGE-A4 mRNA levels. In addition, ADP-A2M4 cells elicited a strong IFNγ response against a primary melanoma tissue material expressing high MAGE-A4 mRNA and protein expression levels. Since no adequate models to define the threshold of ADP-A2M4CD8 activation are currently available, this protocol will be using a conservative cutoff (≥2+ in ≥ 30% of tumor cells) to ensure sufficient expression of the antigen.

To ensure that the subject's tumor has the potential to be targeted by ADP-A2M4CD8, the tumor specimen will be screened at a central reference laboratory for the expression of MAGE-A4 antigens by IHC using a CLIA-validated Clinical Trial Assay. Subjects will be screened for the

presence of MAGE-A4 expression on their tumor through the Screening Protocol (ADP-0000-001).

4.2.2. T Cell Manufacturing

ADP-A2M4CD8 is autologous CD4 and CD8 T cells engineered with an affinity-enhanced TCR to target the tumor antigen MAGE-A4. Autologous T cells are obtained from eligible subjects who have antigen positive tumors and who have appropriate HLA-A. The CD4 and CD8 T cells are transduced with a SIN lentivirus vector expressing the CD8α_MAGE-A4 (affinity enhanced clone c1032) under GMP conditions. The product of this transduction is polyclonal T cells that are designed to target MAGE-A4 in tissue. The transfer SIN lentiviral vector has been meticulously designed to contain only the minimal genetic elements required for function and no vector proteins for maximum biosafety [Dull, 1998]. Many reports provide evidence supporting the relative biosafety of SIN lentiviral vectors in terms of genotoxicity, resulting primarily from the lack of enhancer activity in the lentivirus long terminal repeat (LTR) in comparison to the γ retroviral vectors [Montini, 2006; Maruggi, 2009; Modlich, 2009; Montini, 2009].

Cell product is typically ready to be returned to the site within one month after the start of manufacturing. Receipt of T cell product at the clinical site is required before the start of lymphodepleting chemotherapy.

4.2.3. Lymphodepletion

Lymphodepletion prior to autologous cell transfer may enhance immune reconstitution by the transferred cells and increase tumor specific responses. Immune reconstitution is enhanced through homeostatic mechanisms that facilitate expansion of T lymphocytes [Baccala, 2005] and facilitate trafficking of the engineered T cells [Pinthus, 2004]. Lymphodepletion also enhances the activity of the adoptively transferred cells via the removal of inhibitory factors such as regulatory T cells [Wolf, 2003] and can activate antigen presenting cells through the induction of inflammatory cytokines and induction of tumor apoptosis with resulting cross-presentation of tumor antigens to T cells.

Evidence suggests that preparation for successful engraftment and expansion of gene modified adoptive cellular therapy depends not just on the depth of cytoreduction but additionally on the specific action of some cytotoxic drugs. Recent studies in lymphoma, chronic leukemia, and acute leukemia using adoptive cellular therapy including a CAR showed increased T cell expansion, persistence and disease-free survival when fludarabine was added in a previously cyclophosphamide-only preparative regimen [Turtle, 2015].

In the clinical study, “A Pilot Study of Genetically Engineered NY-ESO-1 Specific NY-ESO-1^{c259}T in HLA-A2+ Patients with Synovial Sarcoma” (NY-ESO-1, ClinicalTrials.gov Identifier: NCT01343043), several lymphodepleting regimens were investigated. In Cohort 1, lymphodepletion consisted of cyclophosphamide 1800mg/m^2/day administered for 2 days in combination with fludarabine 30mg/m^2/day administered for 4 days; this has demonstrated antitumor activity with 6 of 12 treated patients having an objective response (1CR, 5 PR). In Cohort 4, lymphodepletion was reduced and consisted of cyclophosphamide 600 mg/m^2/day in combination with fludarabine 30 mg/m^2/day both administered daily for 3 days; this has also

demonstrated objective tumor responses in 3 of 11 subjects treated as of November 2017. Though responses were achieved in both Cohort 1 and Cohort 4, there were fewer responders and the duration of response was shorter in Cohort 4. In addition, the median peak expansion of transduced T-cells was lower in Cohort 4 (40,137 vector copies/µg) when compared to Cohort 1 (106,174 vector copies/µg), despite similar transduced cell doses in the two cohorts. The data indicate that higher dose lymphodepletion (i.e., in Cohort 1) is needed to achieve optimal post infusion peak expansion and durable responses. Furthermore, treatment was well tolerated in both cohorts [D'Angelo, 2019]. Related AEs ≥ Grade 3 were reported in a higher proportion in Cohort 1 as compared to Cohort 4, but the safety and tolerability was acceptable in both. In both cohorts, the most frequent AEs were cytopenias likely attributable to the lymphodepleting chemotherapy. There were no Grade 5 AEs in either cohort.

Based on the experience using combination fludarabine-cyclophosphamide lymphodepleting chemotherapy in the NY-ESO-1 study (NCT01343043) and the increasing evidence that fludarabine is a key component of the adoptive T cell therapy, the lymphodepleting regimen in this study consists of intravenous (IV) fludarabine 30 mg/m^2/day for 4 days (Day -5 through Day -2) and cyclophosphamide 1800 mg/ m^2/day for 2 days (Days -3 to -2). This lymphodepleting regimen has previously demonstrated acceptable safety and efficacy in a study of NY-ESO-1^{c259}T by Araujo (2019) in subjects with advanced synovial sarcoma (Section 2.2.1).

4.2.4. Long-Term Follow-Up

Subjects exposed to gene therapies may be at risk for delayed AEs when there is persistent biological activity. Contributing factors for delayed AEs include persistence of viral vector, integration of genetic material into host genome, prolonged expression of transgene and alterations in the expression of host genes. The long term follow up (LTFU) evaluation in the study is designed to adhere to the FDA and EMA guidance for long term follow up of subjects in gene therapy clinical trials [FDA, 2006a; FDA, 2006b; FDA, 2010; EMA, 2009], and involves monitoring of subjects who have been exposed to lentivirus-mediated gene transfer in this clinical study for 15 years. If a subject receives a second T cell infusion, the clock restarts with the second infusion and will be followed for 15 years from the time of second T cell infusion. Further information on the safety monitoring for the theoretical risks associated with the use of lentiviral vectors and potential for insertional oncogenesis, as well as safety monitoring are available in Section 8.5.8 and Section 10.6, Appendix 6.

4.3. Justification for Dose

The dose escalation schema will begin at the lowest dose range that has the potential to be efficacious and is believed to be safe based on preclinical data. This is supported by prior studies using CAR-T cells in which the National Institutes of Health (NIH) Recombinant DNA Advisory Committee established the principle that selecting a dose that would be relatively safe but have potential biological activity is an appropriate goal for early stage research [Ertl, 2011].

The initial dose selected for ADP-A2M4CD8 is 0.8×10^9-1.2×10^9 transduced cells to be escalated to 1.2×10^9 - 3×10^9 and then to 3.0×10^9 - 6.0×10^9 transduced cells in a modified 3 + 3 dose escalation scheme (Section 6.4). To date, doses ranging from 0.1×10^9 to 10×10^9 ADP-A2M4 cells have been used in the clinic. Post infusion peak expansion of ADP-A2M4 cells

was low and persistence was transient at doses below 1×10^9, providing no potential for biological activity. Although the target antigen for both ADP-A2M4 and ADP-A2M4CD8 is MAGE-A4, the effect of the CD8α modification in humans is unknown. Therefore, to maintain a positive benefit: risk balance the starting dose in the study was selected to be potentially efficacious but well below the tolerated doses with ADP-A2M4.

The proposed starting dose range is further supported by experience with of NY-ESO-1^{c259}T in patients with synovial sarcoma. Subjects received a median-infused NY-ESO-1^{c259}T cell dose of 3.6×10^9 (range, 0.45×10^9 to 14.4×10^9) transduced cells [Araujo, 2019]. Two subjects who received a dose below 1×10^9 did not show a response and had progressive disease (PD) by Week 12 post infusion, indicating that responses are more likely to be observed at doses at or above 1×10^9 transduced T cells. Treatment demonstrated a manageable toxicity profile across all doses and no correlation between dose and the incidence of AEs has been identified.

Once the tolerability and safety of the lymphodepletion regimen and cell dose has been demonstrated, the dose range will be increased up to maximum of 10×10^9 transduced cells in the Expansion phase (up to 30 subjects). This dose range falls within the overall range that has been effective and safe in clinical trials and allows for acceptable expansion and persistence of the transduced cells as noted in other TCRs to date.

4.4. End of Study Definition

The study will be considered complete once all subjects complete 15 years of follow-up, die, or withdraw early from the study.

5. STUDY POPULATION

Subjects will be assessed for and must meet eligibility for study participation prior to leukapheresis (i.e., at Screening) AND prior to lymphodepleting chemotherapy (i.e., at Baseline).

5.1. HLA and Antigen Pre-screening

To be eligible subjects must be aged ≥18 years with a diagnosis of advanced (metastatic or inoperable) tumors. Subjects identified by the Investigator as possible candidates for the study must have completed screening under the Screening Protocol (ADP-0000-001) and have the appropriate HLA and tumor antigen status. Only subjects that are HLA-A*02 positive, and negative for protocol specified exclusionary alleles, and whose tumor expresses the MAGE-A4 antigen above the cut-off according to the applied IHC are eligible for this study.

5.2. Inclusion Criteria

1. Subject (or legally authorized representative) has voluntarily agreed to participate by giving written Informed Consent in accordance with ICH GCP guidelines and applicable local regulations.
2. Subject has agreed to abide by all protocol-required procedures including study related assessments, and management by the treating institution for the duration of the study including long term follow-up.
3. Age ≥18 years at the time the Pre-screening Informed Consent is signed.
4. Histologically or cytogenetically confirmed diagnosis of any one of the following cancers:

   (A) urothelial cancer (B) melanoma, (C) ovarian cancer, (D) esophageal (squamous and adenocarcinoma) (E) esophagogastric junction (EGJ) cancer, (F) gastric cancer, (G) non-small cell lung carcinoma (NSCLC) (H) head and neck (I) synovial sarcoma or (J) myxoid/round cell liposarcoma (MRCLS).
5. Measurable disease according to RECIST v1.1 prior to leukapheresis and lymphodepletion.
6. Subject must receive ADP-A2M4CD8 as the next therapy following leukapheresis.
   a. Bridging therapy is discouraged. However, if in the opinion of the Investigator, the subject requires immediate therapy after leukapheresis, the subject may receive bridging therapy for the period during which the subject is awaiting the manufacture of ADP-A2M4CD8.
   b. Following this bridging therapy, the subject must adhere to the mandatory washout periods (Section 5.3) and must continue to have measurable disease prior to receiving ADP-A2M4CD8.
7. Subject has the following disease specific requirements for their tumor type. (NOTE: bridging therapy is not considered a prior systemic therapy).
   a. Urothelial Carcinoma
      – Histologically or cytologically confirmed urothelial carcinoma (including mixed histologies of urothelial carcinoma with elements of other subtypes) of the renal

pelvis, ureter, bladder, or urethra with metastatic or unresectable locally advanced disease
  - Prior therapy requirements:
    - Subjects must have received or refused 1 prior platinum-based therapy for the treatment of metastatic or locally advanced unresectable disease.
    - Subjects who are not eligible for a platinum-containing regimen or who have progressed on a platinum-containing regimen may have received an anti-PD-l/PD-L1 checkpoint inhibitor
    - Subjects may have received no more than three prior systemic regimens which may include investigational therapies

b. Melanoma
  - Histologically or cytologically confirmed melanoma with metastatic or unresectable locally advanced disease
  - Prior therapy requirements:
    - Subjects must have received a BRAF inhibitor as monotherapy or in combination with a MEK inhibitor for *BRAF* V600E mutant melanoma
    - Subjects must have received or refused an anti-PD-1/ PD-L1 as monotherapy or in combination with an anti-CTLA-4 inhibitor
    - Subjects may have received no more than three prior systemic regimens which may include investigational therapies

c. Ovarian Carcinoma
  - Histologically or cytologically confirmed ovarian carcinoma (including epithelial ovarian, primary peritoneal, or fallopian tube carcinoma) with disease progression
  - Prior therapy requirements:
    - Subjects must have received no more than 3 prior systemic therapies which may include investigational therapies. One regimen must have been a prior platinum-based chemotherapy regimen for primary disease, possibly including intra-peritoneal therapy, consolidation, biologic/targeted (non-cytotoxic agents, or extended therapy (maintenance/consolidation) administered after surgical or non-surgical assessment. Maintenance therapy is not considered a prior systemic therapy.
    - Subjects must have progressed ≤12 months after completion of their last platinum-based chemotherapy. The number of months (platinum-free interval) should be calculated form the date of the last administered dose of platinum therapy to the date of documentation of progression.
    - Subjects should have received or refused a PARP inhibitor for BRCA mutant ovarian cancer if indicated

d. Esophageal, Esophagogastric Junction (EGJ), and Gastric Carcinoma
  - Histologically or cytologically confirmed esophageal (squamous or adenocarcinoma), EGJ, or gastric carcinoma with metastatic or unresectable locally advanced disease
  - Prior therapy requirements:
    - Subjects must have received a fluoropyrimidine (fluorouracil or capecitabine) and/or platinum regimen.

- Subjects whose tumors are known to be HER2 positive must have failed (progressive disease or unacceptable toxicity) or refused trastuzumab
- Subjects may have received no more than three prior systemic regimens which may include investigational therapies

e. NSCLC
- Histologically or cytologically confirmed advanced NSCLC (squamous cell, adenocarcinoma, adenosquamous, or large cell carcinoma) with metastatic or unresectable locally advanced disease
- Prior therapy requirement:
  - Subjects whose tumor is known to have EGFR mutations or ALK gene rearrangements must have received a prior EGFR or ALK inhibitor, respectively.
  - Subjects whose tumor is known to have a *ROS1* rearrangement or BRAF V600E mutation must have received a *ROS1* or *BRAF* inhibitor, respectively
  - Subjects must have received or refused PD1/L1 monotherapy or combination therapy with chemotherapy.
  - Subjects who have not received an anti-PD-1/L1 therapy as first-line therapy for metastatic disease, must have received or refused anti-PD-1/L1 therapy as second line therapy
  - Subjects may have received no more than three prior systemic regimens which may include investigational therapies. Targeted therapy for EGFR/BRAF V600E mutations or ALK/ROS1 rearrangements are not considered part of these three systemic regimens.

f. Head and Neck Carcinoma
- Histologically or cytologically confirmed head and neck carcinoma with metastatic or unresectable locally advanced disease
- Prior treatment requirement:
  - Subjects must have received or refused a platinum containing chemotherapy regimen for treatment of primary tumor in adjuvant, locally advanced, or metastatic settings.
  - Subjects may have received no more than three systemic regimens which may include investigational therapies.

g. Synovial Sarcoma and Myxoid Liposarcoma/Myoxid Round Cell Liposarcoma
- Histologically or cytologically synovial sarcoma or high grade myxoid liposarcoma / myxoid round cell liposarcoma with metastatic or unresectable locally advanced disease
- Prior treatment requirements:
  - Subjects must have previously received either an anthracycline or ifosfamide containing regimen.
  - Subjects who are intolerant to both anthracycline and ifosfamide must have previously received at least one systemic therapy
  - Subjects may have received no more than three prior systemic regimens which may include investigational therapies

8. HLA-A*02 positive.
9. Tumor (either an archival specimen or a fresh biopsy) shows MAGE-A4 expression defined as ≥30% of tumor cells that are ≥2+ by immunohistochemistry. All samples must have been pathologically reviewed by an Adaptimmune designated central laboratory confirming expression.
10. Subject has an Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1.
11. Left ventricular ejection fraction (LVEF) ≥50% or the institutional lower limit of normal range, whichever is lower.
12. Fit for leukapheresis and adequate venous access can be established for the cell collection.
13. Female subject of childbearing potential (FCBP) must have a negative urine or serum pregnancy test AND must agree to use an effective method of contraception starting at the first dose of chemotherapy and continue for at least 12 months or 4 months after the gene modified cells are no longer detected in the blood, whichever is longer.

    - OR -

    Male subjects must be surgically sterile or agree to use a double barrier contraception method or abstain from heterosexual activity with a FCBP starting at the first dose of chemotherapy and continuing for 4 months thereafter (or longer if indicated in the country specific monograph/label for cyclophosphamide).
14. Subject must have adequate organ function as indicated by the laboratory values in the table below:

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	$\geq 1 \times 10^9$/L (without G-CSF support)
Platelets	$\geq 75 \times 10^9$/L (without transfusion support within 7 days prior to leukapheresis and lymphodepletion)
Hemoglobin	$\geq$ 80 g/L (without transfusion support within 7 days prior to leukapheresis and lymphodepletion)
Coagulation	
Prothrombin time or INR	$\leq 1.5 \times$ upper limit of normal (ULN) unless receiving therapeutic anticoagulation.
Partial thromboplastin time (PTT)	$\leq 1.5 \times$ upper limit of normal (ULN) unless receiving therapeutic anticoagulation.
Renal	
Glomerular filtration rate (estimated or calculated)[1]	$\geq$ 40 mL/min
Hepatic	
Serum total bilirubin	$\leq 1.5 \times$ ULN (unless subject has documented Gilbert's Syndrome with direct bilirubin <35% of total bilirubin)
Alanine aminotransferase (ALT) /serum glutamic pyruvic transaminase (SGPT)	$\leq 2.5 \times$ ULN
[1] Renal function (GFR) will be estimated or measured according to standard practice at the treating institution. Renal function will be reassessed at Baseline using the same methodology	

5.3. Exclusion Criteria

1. HLA-A genotype (The Sponsor will review the results of HLA typing for inclusion and exclusion alleles and will adjudicate subject eligibility based on HLA results):
    - HLA-A*02:05 positive in either allele.
    - No HLA-A*02 allele other than A*02:07 or any A*02 null allele (designated with an "N" suffix, e.g. A*02:32N)
2. Subject has received or plans to receive the following therapy/treatment prior to leukapheresis or lymphodepleting chemotherapy, unless stopped according to the wash-out requirements:

Treatment/Therapy	Required Wash-out Prior to Leukapheresis	Required Wash-out Prior to Lymphodepletion
Cytotoxic chemotherapy	3 weeks	3 weeks
Small molecules/tyrosine kinase inhibitor (TKI) such as dabrafenib, trametinib, vemurafanib and cobimetinib. NOTE: No	1 week	1 week

Treatment/Therapy	Required Wash-out Prior to Leukapheresis	Required Wash-out Prior to Lymphodepletion
washout period is required for compounds that do not cause bone marrow suppression/lymphopenia or for EGFR and ALK/ROS-1 inhibitors		
Immune therapy (including monoclonal antibody therapy, checkpoint inhibitors, biologics)	2 weeks	2 weeks
Experimental anticancer vaccine	N/A	2 months in the absence of tumor response. The subject should be excluded if their disease is responding to an experimental vaccine given within 6 months
Gene therapy using an integrating vector	Any use of previous gene therapy using an integrating vector is not permitted	Any use of previous gene therapy using an integrating vector is not permitted
Corticosteroids or any other immunosuppressive therapy. NOTE: Use of topical or inhaled steroids is not an exclusion. See Section 6.6.1 for exceptions.	2 weeks	2 weeks
Investigational treatment	2 weeks or 5 half-lives, whichever is shorter	2 weeks or 5 half-lives, whichever is shorter
Radiation to vital organs (e.g. liver, kidney)	N/A	4 weeks
Radiation to the pelvis	4 weeks	4 weeks
Whole brain radiotherapy (WBRT) or brain stereotactic radiosurgery (SRS)	N/A	2 weeks
Radiotherapy to the target lesions	N/A	A lesion with progression post-radiotherapy may be considered a target lesion. (NOTE: there is no washout period for palliative radiation to non-target organs).
NOTE: Duration of any other anticancer therapies must be discussed with the Sponsor Study Physician		

3. Toxicity from previous anticancer therapy must have recovered to ≤ Grade 1 or baseline prior to enrollment (except for non-clinically significant toxicities, e.g., alopecia, vitiligo). Subjects with Grade 2 toxicities that are deemed stable or irreversible (e.g. peripheral neuropathy) can be enrolled.
4. History of allergic reactions attributed to compounds of similar chemical or biologic composition to fludarabine, cyclophosphamide or other agents used in the study.
5. History of autoimmune or immune mediated disease. Subjects with hypothyroidism, diabetes, adrenal insufficiency or pituitary insufficiency that are stable on replacement therapy are eligible. Subjects with disorders such as asthma, psoriasis or atopic dermatitis that are well controlled without requiring systemic immunosuppression are also eligible.

6. Subject had major surgery within 4 weeks prior to lymphodepletion; subjects should have been fully recovered from any surgical related toxicities.
7. Leptomeningeal disease, carcinomatous meningitis or symptomatic CNS metastases. Subjects with a prior history of symptomatic CNS metastases must have received treatment (i.e., stereotactic radiosurgery (SRS), whole brain radiation (WBRT) or surgery) and be neurologically stable for at least 1 month, not requiring anti-seizure medications and off of steroids for at least 14 days prior to leukapheresis and lymphodepletion. Subjects who have asymptomatic CNS metastases without associated edema, shift, requirement for steroids or anti-seizure medications are eligible. If such a subject receives SRS or WBRT, a minimum period of 2 weeks needs to lapse between the therapy and lymphodepletion. Prophylactic anti-seizure medication is allowed.
8. Other prior malignancy that is not considered by the Investigator to be in complete remission. Resectable squamous or basal cell carcinoma of the skin is acceptable.
9. Electrocardiogram (ECG) showing clinically significant abnormality at Screening
10. Uncontrolled intercurrent illness including, but not limited to:
    - Ongoing or active infection;
    - Clinically significant cardiac disease defined by congestive heart failure New York Heart Association (NYHA) Class 3 or Class 4;
    - Uncontrolled clinically significant arrhythmia;
    - Acute Coronary Syndrome (ACS) (angina or MI) in last 6 months;
    - Clinically significant pulmonary disease with pulmonary function with parameters <60% predicted (FEV1 and DLCO) assessed prior to leukapheresis or with a requirement for home oxygen
    - Interstitial lung disease (pneumonitis), history of pneumonectomy, or of COPD with ≥ one exacerbation within 1 year prior to the Screening visit that required treatment with systemic corticosteroids or resulted in hospitalization.
11. Active infection with human immunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis C virus (HCV), or human T cell leukemia virus (HTLV) as defined below:
    - Positive serology for HIV;
    - Active hepatitis B infection as demonstrated by test for hepatitis B surface antigen. Subjects who are hepatitis B surface antigen negative but are hepatitis B core antibody positive must have undetectable hepatitis B DNA and receive prophylaxis against viral reactivation. Prophylaxis should be initiated prior to lymphodepleting therapy and continued for 6 months;
    - Active hepatitis C infection as demonstrated by hepatitis C RNA test. Subjects who are HCV antibody positive will be screened for HCV RNA by any RT PCR or bDNA assay. If HCV antibody is positive, eligibility will be determined based on a negative screening RNA value;

- Positive serology for HTLV 1 or 2;
- Re-screening for infectious disease markers is not required at baseline (prior to lymphodepletion) unless > 6 months has elapsed.

12. Pregnant or breastfeeding.
13. In the opinion of the Investigator, the subject is unlikely to fully comply with protocol requirements.

5.4. Additional Eligibility Criteria (Prior to Second T-Cell Infusion)

Subjects treated in all groups may receive a second infusion during the Expansion phase of the study (Section 6.3.3). Prior to receipt of a second T-cell infusion, all subjects must remain eligible to receive manufactured T-cell product as defined in Section 5.2 and Section 5.3 and meet the following inclusion criteria:

1. Subject has had a documented confirmed response (PR or CR) or clinical benefit ≥ 4 weeks after the first T-cell infusion.
   a. Subjects with a CR or PR will not be eligible for a second infusion until PD.
   b. Subjects with stable disease (SD) or PD (per RECIST or evidence of clinical progression) may be considered for a second infusion after discussion with the Sponsor.
2. A second T-cell infusion is recommended by the Investigator.
3. Subject has a new tumor biopsy confirming MAGE-A4 expression.
4. Subject has voluntarily agreed to receive a second T-cell infusion by giving written informed consent.
5. All toxicities from the first T-cell infusion have resolved to Grade ≤1.
6. Manufactured T-cell product is available.
   - In cases where previously manufactured T-cell product is not available, any residual leukapheresis product from collections prior to receipt of the gene modified T cells will be utilized for a new product manufacture.
   - In cases where residual leukapheresed product is not available, subjects can agree to be re-leukapheresed for cells only in circumstances where there are no detectable gene modified cells.

A subject meeting the following criterion is not eligible for a second T-cell infusion:

1. Subject has clinically life-threatening (Grade 4) AEs deemed at least possibly related to the ADP-A2M4CD8 T-cell product by the Investigator and study Sponsor reported during the first T-cell infusion unless agreed upon by the SRC.

5.5. Screen Failures

A screen failure log documenting the Investigator's assessment of each screened subject with regard to the protocol inclusion and exclusion criteria is to be maintained by the Investigator.

Subjects may be re-tested for eligibility criteria, during which time subjects will stay within the screening period of the treatment protocol until the criteria is either met or not met before recruitment closes.

5.6. Number of Subjects and Study Duration

Up to 30 total subjects will be enrolled to evaluate clinical benefit:risk in subjects who received the ADP-A2M4CD8 therapy.

Study enrollment is expected to continue for approximately 18 months.

Clinical cut-off to evaluate safety and antitumor activity will occur once all subjects in the Interventional Phase have either experienced disease progression or have been followed-up for at least 6 months post-initial T-cell infusion. At this time, all safety and secondary efficacy endpoints will be summarized to provide supportive evidence to the primary assessment.

5.7. Sites

The study will be conducted in approximately 15 sites. The number of centers is necessary to ensure recruitment in this rare patient population. Additional sites may be added at the discretion of the Sponsor.

6. STUDY INTERVENTION

6.1. Leukapheresis

Subjects who complete screening procedures defined in the Screening Protocol (ADP-0000-001) and who meet all eligibility criteria defined in Section 5.2 and Section 5.3 will be eligible to undergo leukapheresis to obtain starting material for the manufacture of autologous ADP-A2M4CD8.

Refer to the Apheresis and T Cell Product Manual for scheduling of apheresis.

A non-mobilized PBMC collection should be performed by an apheresis unit at the enrolling institution according to the institution's or hospital's policies and procedures. Bilateral peripheral venous access should be used whenever possible but a temporary central venous catheter (CVC) may be placed for collection if peripheral venous access is inadequate. Standard clinical procedures for apheresis should be followed.

A large volume leukapheresis should be performed. For subjects who are >50 kg, 10 to 15 liters should be processed per procedure; in subjects ≤50kg, 2 to 3 blood-volumes should be processed per procedure with a goal of the procedure being collection of 1.0×10^8 PBMC/kg, and a minimum of 1.5×10^7 PBMC/kg. In cases where the minimum number of PBMC is not collected or the T cells cannot be administered (e.g., release criteria not met), a second apheresis may be performed. Citrate anticoagulant should be used. Prophylactic IV $CaCl_2$ and $MgSO_4$ infusions should be administered at the discretion of the apheresis physician.

The collected leukapheresis product should be labelled and transported for manufacture as detailed in the Apheresis and T Cell Product Manual.

Any remaining subject apheresis material that is not required for further manufacture of ADP-A2M4CD8 for either a subject's first or second (if applicable) infusion may be used by the Sponsor for research to modify or improve the manufacturing process and to enhance the clinical response.

6.2. Lymphodepleting Chemotherapy

Prior to the administration of lymphodepleting chemotherapy all eligibility criteria will be reconfirmed and a baseline tumor biopsy obtained.

Once the manufactured ADP-A2M4CD8 product has been received at the clinical site and the integrity of the bag(s) has been verified by the site, eligible subjects will proceed to have lymphodepleting chemotherapy with fludarabine and cyclophosphamide as described in Table 3. Dose justification for the lymphodepletion regimen is described in Section 4.2.3.

The lymphodepleting chemotherapy may be given as an outpatient treatment, or subjects may be hospitalized at the discretion of the Investigator.

On admission of subject for lymphodepleting chemotherapy, commence antimicrobial and antifungal prophylaxis (Section 10.4.3) in line with institutional guidelines.

Appropriate IV hydration should be administered and Mesna should be given to prevent urotoxicity while cyclophosphamide is administered, as described in Table 3. Other premedication (e.g., anti-emetics) may also be provided in accordance with institutional standards. Steroids may be used as anti-emetics for cyclophosphamide but must be discontinued no later than Day -3.

Table 3: Fludarabine and Cyclophosphamide Treatment Schema

Lymphodepleting Chemotherapy				
Day	**Drug**	**Dose**	**Route**	**Administration**
-5	Fludarabine[1]	30 mg/m^2	IV	in 50 to 100mL 0.9% NaCl over 30 mins[2,3]
-4	Fludarabine[1]	30 mg/m^2	IV	in 50 to 100mL 0.9% NaCl over 30 mins[2,3]
-3	Fludarabine[1]	30 mg/m^2	IV	in 50 to 100mL 0.9% NaCl over 30 mins[2,3]
	Cyclophosphamide	1800 mg/m^2	IV	in 200 to 500mL0.9% NaCl over 2 hours[2,3]
-2	Fludarabine[1]	30 mg/m^2	IV	in 50 to 100mL 0.9% NaCl over 30 mins[2,3]
	Cyclophosphamide	1800 mg/m^2	IV	in 200 to 500 mL0.9% NaCl over 2 hours[2,3]
1	ADP-A2M4CD8 infusion[5]			
3	Start G-CSF[3,4]			

[1] Fludarabine dose will be adjusted for renal impairment as described in Section 6.2.1
[2] Concentration of 1mg/ml or less
[3] Begin G-CSF on Day 3 and continue as per Section 6.2.3. Long-acting (pegylated) G-CSF may be given instead of short acting G-CSF according to institutional standard practice. If pegylated G-CSF is administered, give one dose on Day 3 post infusion.
[4] Administration of Mesna described Section 6.2.2 and G-CSF in Section 6.2.3
[5] Administration of ADP-A2M4CD8 infusion is described in Section 6.3.

6.2.1. Fludarabine Dose Adjustment for Renal Impairment

Dose of fludarabine will be adjusted for subjects with renal dysfunction as follows:

Creatinine clearance	**Fludarabine dose**
≥80 mL/min	30 mg/m^2
40 – 79 mL/min	20 mg/m^2

6.2.2. Mesna

Mesna may be given to prevent urotoxicity per institutional guidelines or as recommended below:

- 360 mg/m^2 (20% cyclophosphamide dose) as an IV bolus at the start of cyclophosphamide, 3, 6, and 9 hours post infusion on each day of cyclophosphamide administration

6.2.3. G-CSF

The pre-conditioning chemotherapy is intended to cause lymphodepletion. However, neutropenia is also common. It is recommended that G-CSF is given daily from Day 3 post-infusion of ADP-A2M4CD8 until resolution of neutropenia in accordance with ASCO guidelines or institutional standard practice. Long-acting (pegylated) G-CSF may be given instead of short acting G-CSF according to institutional standard practice. If pegylated G-CSF is administered, give one dose on Day 3 post infusion of ADP-A2M4CD8.

While the use of G-CSF is strongly advised, the final decision on its use is left to the discretion of the Investigator.

6.3. Investigational Product

6.3.1. Premedication

Thirty to 60 minutes prior to cell infusion, subjects will be premedicated against potential infusion reactions with antihistamines and acetaminophen (paracetamol) according to institutional practice. NOTE: Steroids should not be administered as premedication for T-cell infusion because they are lymphotoxic and inhibitory to the T cell product. Steroids may be used as anti-emetics for cyclophosphamide but must be discontinued no later than Day -3.

6.3.2. T Cell Infusion

On Day 1, the subject will receive thawed ADP-A2M4CD8 by intravenous infusion. During the dose escalation phase of the study it is required that the T-cell infusion is given as an inpatient procedure and that subjects are hospitalized for at least 72 hours following dosing. This allows for close monitoring of post-infusion AEs during the dose escalation phase of the study. The subject may be discharged thereafter if medically stable at the discretion of the Investigator. During the dose Expansion phase, subjects may be hospitalized at the discretion of the Investigator.

Prior to infusion, two clinical personnel in the presence of the subject, will independently verify and confirm that the information on the infusion bag is correctly matched to the subject, as per the Apheresis and T-cell Manual.

The T-cell product must not be thawed until immediately prior to infusion. The T-cell product should be thawed at a set temperature of 37^{o}C using a water bath or equivalent device. Routinely the cells should be thawed for approximately 3 to 5 minutes. Smaller volumes may take less time

to thaw. The infusion bags should be observed during the thaw process to ensure no frozen material or ice remains.

The infusion bag(s) may be placed into a secondary containment bag per institutional standard procedures. The secondary containment bag should not be of a design where it will have to be cut open after use, so as to avoid sharp objects near the infusion bag. A standard specimen bag with a re-sealable zipper closure is recommended.

The cells can be thawed either at the subject's bedside or in a centralized facility, according to institutional standard procedures. If the cells are transported from a central storage location to bedside for thawing, it is recommended to place the bag(s) on dry ice or in a cooler with frozen gel packs for transport. If the cells are thawed at a central facility, the thawed cells should be transferred to bedside under 2°C to 8°C conditions and must be transported by appropriately trained staff to preserve the chain of custody.

The infusion should begin within 10 minutes of completing thaw (per bag) and is recommended to complete infusion within 45 minutes of thawing each bag to minimize exposure of the cell product to cryoprotectant. If the cells are provided in multiple bags and thawed at the bedside, the second bag should not be thawed until half the first has been infused without reaction, if possible based on fill volume. Bags thawed in a central location they may be thawed simultaneously with consideration given to transport time and the guidance to begin infusion within 10 minutes post-thaw.

If after thawing the infusion bag is damaged or leaking, the Principal Investigator (PI) and Sponsor should be notified and the cells should not be infused.

The T-cell product must not be washed or otherwise processed. It is recommended that the T-cell product is administered using a dual spike infusion set by gravity over 15 to 45 minutes in the absence of infusion reaction. Cells should ideally be infused without a filter, however if a filter is required by Institutional practice the pore size must not be smaller than 170 µm. Infusion pumps must not be used. For administration of the cells, 100 to 250 mL of 0.9% sodium chloride should be connected to the second lumen of the infusion set, used to prime the line, and then the lumen closed. On completion of the infusion of a bag of T-cell product, the main line should be closed and approximately 50 mL saline transferred into the cell bag, and then infused to minimize the loss of cells. This process should be repeated for each cell bag if multiple bags are provided.

On completion of the cell infusion the set should be flushed using additional saline from the attached bag. In the event that Institutional practice requires a single spike infusion set (e.g., macro drip IV tubing) standard institutional guidelines for the infusion of autologous cell infusion should be followed. The line must be flushed with 0.9% sodium chloride once the infusion is complete.

In the event of adverse reaction to the cell infusion, the infusion rate should be reduced, and the reaction managed according to institutional standard procedures. Steroid treatment should be avoided unless medically required. In the event a subject develops a febrile episode following the infusion, appropriate cultures and medical management should be initiated, with attention to the initiation of empirical antibiotic treatment in the case of febrile neutropenia (Section 10.4.1).

The day of T-cell infusion may be delayed in subjects with significant complications of chemotherapy if according to the Investigator it is in the best interest of the subject. Cytopenias alone should not be a reason to delay T-cell infusion unless complications are present. Subjects who have undergone leukapheresis but do not receive the T-cell infusion will be replaced. Subjects who undergo leukapheresis and do not receive T-cells will be followed for safety events for 30 days post leukapheresis or until SAEs have resolved to Grade 1 or baseline, whichever is longer.

The timing of all assessments post-infusion will be calculated with reference to the T- cell infusion date. Vital signs will be recorded prior to the infusion and at 5, 15, and 30 minutes and at 1, 1.5, 2, and 4 hours after the infusion has started.

Discharge from hospital post-T-cell infusion will be at the discretion of the Investigator. All subjects must be reviewed by the Investigator (or a designated study physician) prior to discharge.

6.3.3. Second T-Cell Infusions

Following the initial infusion, subjects who have had a documented confirmed response (PR and CR) or clinical benefit ≥4 weeks after the first T-cell infusion and whose tumors continue to express MAGE-A4 as verified by assay performed in biopsied tissue, can be considered for a second infusion with engineered T-cells. Subjects must continue to meet all eligibility criteria for the study in addition to those specified in Section 5.4 prior to receiving a second infusion. Subjects with a CR or PR will not be eligible for second infusion until PD. Subjects with SD or PD (per RECIST or evidence of clinical progression) may be considered for a second infusion after discussion with the Sponsor.

The second infusion may be given within 6 months of PD and after at least 8 weeks have elapsed from the time of previous infusion. During the period in which the subject is being considered for a second infusion, new or changes in AEs as defined in Section 8.5 must be recorded in the electronic data capture (EDC) system and blood for persistence (for safety) and RCL monitoring must be collected at the time points noted in the Main T&E (Table 1). However, no other clinical assessments or procedures are required until the subject is consented for the second infusion.

Some subjects may need to have another leukapheresis. Prior to Screening subjects for the second T-cell infusion, it should be determined if the subject has either 1) previously manufactured T-cell product available or 2) any residual leukapheresis product that can be utilized for a new T-cell product manufacture. In cases where T-cell product or leukapheresed product is not available, the subject can agree to undergo another leukapheresis for cells only in circumstances where there are no detectable gene modified cells. For subjects who do require another leukapheresis, please follow the clinical procedures and assessments noted in Table 1 from the Screening visit onwards, with the exception of the following procedures at Screening which are not required.

- Demographics
- Tumor type
- Tumor biopsy at Baseline

For subjects who do not require another leukapheresis, follow the clinical procedures and assessments noted in Table 1 from the Baseline visit onwards.

NOTE: If a fresh biopsy was taken to confirm continued expression of MAGE-A4 at the time of PD after the first T-cell infusion and there is sufficient tumor sample left remaining, this sample may be used as the baseline sample for the second infusion. Otherwise, the baseline biopsy may be collected anytime between two months and one week prior to the start of lymphodepleting chemotherapy, with preference closer to the time of infusion.

While any subject in dose escalation or Expansion may be a candidate for a second infusion, the subject may not receive the second infusion until dose escalation has been completed and Group 3 subjects have cleared the DLT period. The dose of the subject's second infusion will be the dose administered in the Expansion group as indicated in Section 6.4.

6.4. Dose Escalation

The initial dose selected for ADP-A2M4CD8 is 0.8×10^9 - 1.2×10^9 transduced cells to be escalated to 1.2×10^9 - 3×10^9 and then to 3.0×10^9 - 6.0×10^9 transduced cells in a modified 3 + 3 dose escalation scheme (Table 4). Once the tolerability and safety of the lymphodepletion regimen and cell dose has been demonstrated, the dose range will be increased up to a maximum of 10×10^9 transduced cells in the Expansion phase (up to 30 subjects including dose escalation groups). This dose range falls within the overall range that has been effective and safe in clinical trials of other TCRs to date. ADP-A2M4CD8 will be administered by a single IV infusion.

Table 4: Cell Dose Groups

Group	Number of Subjects	Transduced cells[1]	Interval for Safety Review
1	3 to 6	0.8×10^9 to 1.2×10^9	Minimum 14-day observation period after first subject prior to the start of lymphodepletion in the second and third subjects [2]
2	3 to 6	1.2×10^9 to 3.0×10^9	Minimum 14-day observation period after first subject prior to the start of lymphodepletion in the second and third subjects [2]
3	3 to 6	3.0×10^9 to 6×10^9	Minimum 14-day observation period after first subject prior to the start of lymphodepletion in the second and third subjects [2]
Expansion	Up to 30 (includes dose escalation)	1.0×10^9 to 10×10^9	No predetermined observation period

[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 14 days for the subsequent treated subjects in that group

In Group 1 through 3, initiation of lymphodepleting chemotherapy in the first 3 subjects will be staggered: lymphodepletion of the second and third subjects will occur only after the first subject has completed a minimum observation period of 14 days from T-cell infusion. If there are no DLTs in the first 3 subjects treated in Groups 1 through 3, then dosing can proceed into the next higher dose. 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 14 days for the 3 subsequent treated subjects.

6.4.1. Decision-Making Guidelines for Dose Escalation

Decision-making guidelines for dose escalation are as follows based on the number of subjects developing a DLT:

A) 0 out of 3 subjects; escalate to the next cell dose level

B) 1 out of 3 subjects; enroll 3 additional subjects at the current cell dose level

B1) 1 out of 6 subjects; escalate to the next cell dose level

B2) 2 out of 6 subjects; halt dose escalation and potentially declare previous dose as the Maximum Tolerated Dose (MTD) (if these DLTs were observed in Groups 2 or 3), **or** the Safety Review Committee (SRC, Section 6.4.4) may recommend to add 3 additional subjects at this dose level for a total of 9 subjects to further characterize toxicity.

- If DLT rate remains 2 out 9, the SRC may recommend escalating to the next group.
- A third DLT during cohort expansion to N=9 would result in pausing of dose escalation and the previous dose may be declared the MTD.

B3) >2 out of 6 subjects would result in pausing of dose escalation; the MTD may be declared to be the previous dose.

C) 2 out of 3 subjects; halt dose escalation and potentially declare the previous dose as the MTD (if these DLTs were observed in Groups 2 or 3), **or** the SRC (Section 6.4.4) may recommend to add 3 additional subjects at this dose level for a total of 6 subjects. If no further DLTs are observed (i.e., 2 out of 6 DLT), the SRC will review the data and may recommend to add 3 additional subjects at this dose level for a total of 9 subjects to further characterize toxicity If the DLT rate remains 2 out 9, the SRC may recommend escalating to the next group.

D) 3 out of 3 subjects; dose escalation is halted and the MTD is the previous dose (if these DLTs were observed in Groups 2 or 3).

After initiation of the Expansion phase, safety will continue to be monitored. The SRC (Section 6.4.4) will continue to evaluate the totality of the ADP-A2M4CD8 safety data including predictive probabilities (Section 9) based on adverse events of special interest (AESI) (Grade ≥3 CRS and Grade ≥3 ES) throughout the study (including second infusion) to evaluate whether additional risk management steps are recommended.

6.4.2. Number of Subjects

This is a modified 3 + 3 dose escalation trial with up to 3 dose groups plus Expansion. The sample size of each group is anticipated to be between 3 and 6 subjects, for a total of up to 18 subjects treated during dose escalation. Additional subjects will be dosed in the dose Expansion phase to characterize safety (based on safety review and Bayesian predictive probabilities methods) and efficacy (based on subjects with at least 1 evaluation for response). The overall sample size of the study inclusive of the Expansion phase is up to 30 treated subjects.

6.4.3. Evaluation of Dose-Limiting Toxicity

Each cell dose group will treat a minimum of 3 subjects. Toxicity assessment, including evaluation of DLTs, will be performed using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

A DLT is defined as

- Any clinical toxicity of Grade 3 or higher (using NCI CTCAE v5.0) regardless of the Investigator's assessment of relationship to the gene-modified T-cell infusion

NOTE: The DLT observation period will be during the first 30 days following the first infusion of ADP-A2M4CD8 for each subject in all groups. In evaluating potential DLTs, there may be a toxicity considered clearly attributable to the disease, lymphodepleting chemotherapy regimen, or otherwise clearly unrelated to the T-cell product. For these events, the SRC will assess whether the toxicity is deemed a DLT. Two DLTs in one group will not automatically result in determination of the MTD. For these events, the SRC will convene to assess whether additional subjects may be enrolled. In the event that continued enrollment is allowed by the SRC, this will not result in a change to DLT definitions. See Section 6.4.4 for details of the SRC.

In specific instances, a Grade ≥3 toxicity that occurs beyond 30 days may be considered a DLT by the Investigator after consultation with the Sponsor. Events determined to be DLTs will be reported to the SRC and the Regulatory Authorities, if appropriate, according to the standards for expedited reporting defined in Section 8.5.4.

The following toxicities are **not** considered DLTs:

- Grade 3 or 4 fever
- Grade 3 or 4 febrile neutropenia
- Grade 3 colitis resolving to Grade ≤2 within 7 days
- Grade 3 CRS or toxicities related to CRS resolving to Grade ≤ 2 within 7 days
- Grade 4 CRS or toxicities related to CRS resolving to Grade ≤3 within 2 days; and to Grade ≤2 within 5 additional days
- Grade 3 rash associated with CRS or drug reaction
- Grade 3 diarrhea, nausea, or vomiting resolving to Grade ≤2 with supportive treatment within 3 days after onset

- Grade 3 or 4 hypoalbuminemia or abnormal electrolytes responding to supplementation
- Grade 3 alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) elevation resolving to Grade ≤2 or baseline within 7 days
- Grade 3 anemia
- Grade 3 or 4 leukopenia, lymphopenia or neutropenia
- Grade 3 or 4 thrombocytopenia not associated with significant bleeding
- Grade 3 generalized weakness, fatigue, anorexia, or insomnia resolving to Grade ≤2 within 7 days

6.4.4. Safety Review Committee

A Safety Review Committee (SRC) will be implemented in this study and will consist of at least three external physicians with expertise in oncology and adoptive cell therapies, at least one of whom is unaffiliated to the studies; the Sponsor Pharmacovigilance Physician (this person is not directly involved in the study and will serve as the head of the SRC); the Sponsor Head of Clinical Development, and the Sponsor Head of Statistics. SRC meetings will be conducted approximately monthly provided subjects have been enrolled and data are available to be reviewed. The SRC will review cumulative study safety data and recommend actions regarding cell dose group expansion or dose escalation, study modification for safety reasons, halting and restarting enrollment, study termination, or any other benefit:risk related issues deemed important to study conduct, to the Sponsor. An SRC charter, defining roles and accountabilities and the process for safety review, will be available.

6.5. Preparation, Handling, Storage, and Accountability

6.5.1. Packaging and Labelling

Selected, qualified manufacturing sites will manufacture, package and label cell product for each individual subject in accordance with applicable regulatory requirements.

Refer to the Apheresis and T cell Product Manual for T cell product labelling.

6.5.2. Receipt and Return

Investigational product (IP) must be received by a designated person at the site, handled and stored safely and properly, and kept in a secure location to which only the Investigator and designated site personnel have access. IP is to be dispensed only in accordance with the protocol. The Investigator is responsible for keeping accurate records of the IP received from the Sponsor, the amount dispensed and any unused IP remaining at the conclusion of the study. Contact the Sponsor or designee regarding any questions concerning the IP.

Sites should contact the Sponsor or designee for specific instructions for IP returns or destruction.

6.5.3. Storage and Handling

Manufactured T cell product should arrive on-site and immediately be stored at ≤-130°C in the vapor phase of a liquid nitrogen or a mechanical freezer until the date of infusion. Please refer to the Apheresis and T cell Product Manual for additional information.

6.5.4. Investigational Product Accountability/Traceability

The IP provided for this study is for use only as directed in the protocol. The Investigator/ institution must have an established system for subject and product accountability at the site. The system should contain sufficient detail to allow linking of each product delivered to the Investigator to the subject receiving it and vice versa. The Investigator must ensure:

- Deliveries of IP are correctly received by a responsible person
- Such deliveries are recorded
- IP is handled and stored safely and properly as instructed in the Apheresis and T cell Product Manual
- IP is only administered to study subjects in accordance with the protocol
- IP administration is documented. Records must include the identification of the person to whom the IP was administered, date of infusion, start and stop time of infusion and the amount infused. This record is in addition to any IP accountability information recorded on the electronic Case Report Form (eCRF).
- Any unused IP is accounted for in the sites records before returning to the Sponsor (or designee)

At the end of the study, it must be possible to reconcile IP delivered with records of usage and return/destruction. Any discrepancies must be accounted for on the appropriate forms.

Refer to the Apheresis and T cell Product Manual for additional information.

6.5.5. Alert Cards

All subjects who receive IP in the trial will be provided with an alert card, which has been previously agreed by the Sponsor and approved by the Institutional Review Board (IRB)/Independent Ethics Committee (IEC). Alert cards will contain as a minimum the name of the subject, the Investigator contact number, and information regarding the IP received.

6.6. Concomitant Medications

6.6.1. Prohibited Concomitant Medications

The following treatments are prohibited post-T cell infusion (i.e., prior to disease progression): non-protocol chemotherapy, immune therapy, biological therapy (including targeted therapies with tyrosine kinase inhibitors or monoclonal antibodies), or investigational anticancer therapy. Subjects should also not undergo other anticancer locoregional therapies such as non-palliative radiation.

Subjects who undergo any active anticancer therapy, with the exception of surgical resection prior to disease progression, will be considered as having met the PD criterion for efficacy and will follow the LTFU schedule.

It is preferred that subjects do not undergo surgical resection of tumor lesions during the study prior to disease progression, as it interferes with the assessment of the efficacy of ADP-A2M4CD8. However, if a subject undergoes surgical resection prior to disease progression because their tumor has become resectable, they will continue to be followed for safety and efficacy until disease progression. Upon progression, the subject will follow the LTFU schedule. Subjects who have surgery for new lesions consistent with PD or to control PD in previously identified lesions will discontinue the Interventional Phase and follow the LTFU schedule.

See Section 5.3 for details of washout and excluded treatments prior to leukapheresis or lymphodepleting therapy.

The use of systemic steroids may abrogate the effects of the T cell therapy and should be avoided unless required to manage CRS or ES (see Section 10.4.6 for CRS treatment recommendations) or other significant immune-mediated AEs. According to local standard of care or ASCO guidelines, steroids may be used as anti-emetics before cyclophosphamide but must be discontinued no later than 3 days prior to infusion of the IP (Day -3). Steroid use is permitted for prophylaxis or treatment of contrast dye allergies. Physiological doses of steroids, including stress doses when clinically appropriate, may be administered as replacement therapy in subjects with adrenal insufficiency. Fludrocortisone is permitted. In general, daily prednisone doses of 0.5 mg/kg or lower, or their equivalent for other corticosteroid agents are acceptable, as physiologic replacement provided that the subject continues to meet eligibility criteria (Section 5.2 and Section 5.3). Topical steroids for cutaneous application and inhaled steroidal treatments are permitted.

6.6.2. Permitted Concomitant Medications

Palliative radiation for pain relief to non-measurable lesions or non-target lesions present at baseline is permitted during the study. However, lesion sites requiring radiotherapy after the T cell infusion, should be evaluated as to whether this indicates disease progression and the disease progression recorded in the eCRF.

Other treatment that the Investigator considers necessary for a subject's welfare may be administered during the study at the discretion of the Investigator in keeping with community standards of medical care and in adherence to the protocol. Before immunizing a subject at high risk for vaccine-preventable disease (or a member of the subject's household), consult an Infectious Disease specialist or a guidance such as the CDC Clinical Practice Guideline for Vaccination of the Immunocompromised Host.

All concomitant medications will be recorded with dose and frequency, including all prescription or over-the-counter (OTC) medications and herbal remedies. The following will be recorded on the appropriate eCRF pages:

- All prescription and nonprescription medication, vitamins, herbal and nutritional supplements taken by the subject during the 30 days prior to screening will be recorded at the Screening visit.
- All prior anticancer treatments taken by the subject must be recorded regardless of time.
- All concomitant medications taken while subjects are being followed for efficacy.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/ WITHDRAWAL

7.1. Interventional Phase and Long-Term Follow-Up

A subject will be considered to have ended the Interventional Phase of the study when he/she has received the T-cell infusion(s) and subsequently has PD, has died prior to PD or is withdrawn.

After the Interventional Phase of the study, subjects will continue in LTFU for observation of the emergence of LTFU AEs during the 15 years post-infusion in accordance with FDA and EMA regulations [EMA, 2009; FDA, 2006a] and as described in Section 4.2.4 and Section 10.6.

Subjects being considered for eligibility for second infusion may remain in the Interventional Phase for up to 6 months after progression prior to a second infusion. They will enter LTFU after they are deemed ineligible for second infusion or when they end the Interventional Phase after the second infusion.

A subject will be considered to have ended the study when he/she has been followed for 15 years from time of the last T cell infusion or discontinued the study for any reason.

For the end-of-study definition see Section 4.4.

7.2. Subject Withdrawal

A subject may withdraw from the study at any time for any reason without prejudice to their future medical care by the physician or institution. However, the Investigator must make every reasonable effort to keep each subject on study for the whole duration of the trial. If a subject decides to withdraw from any further study assessments/procedures, the Investigator should ask if the subject is willing for survival data only to be collected, this discussion should be documented in the source notes.

Results of any evaluations and observations, together with a description of the reasons for study withdrawal, must be recorded in the medical records and eCRF.

Subjects who undergo leukapheresis and do not receive T cells will be followed for safety events for 30 days post leukapheresis or until SAEs have resolved to Grade 1 or baseline, whichever is longer. Subjects should not receive lymphodepleting chemotherapy until the cell product has met all release criteria and is at the investigational site; therefore, lymphodepleting chemotherapy should be followed by T cell infusion in all subjects. In the event a subject receives lymphodepleting chemotherapy and does not receive T cell infusion, the subject will be followed for at least 30 days or until all toxicity has improved to at least Grade 1 or baseline, whichever is longer or until no further improvement can be expected.

7.2.1. Ending the Interventional Phase

Reasons that a subject could end the Interventional Phase of the study are:

- Disease progression per RECIST v1.1
- Clinical progression

- Death
- Unable/unwilling to comply with study requirements
- Withdrawal of consent
- Investigator decision
- AE
- Lost to follow-up
- Pregnancy
- Termination of the study by the Sponsor

All subjects, with the exception of those who withdraw consent, die, are lost to follow up or did not receive any T cells, will continue in LTFU for observation of delayed AEs . AEs in subjects who terminate early for any reason (other than withdrawal of consent or lost to follow-up) will be followed-up in accordance with Section 8.5.

In the event a subject receives lymphodepleting chemotherapy and does not receive T-cell infusion, the subject will be followed for at least 30 days or until SAEs have resolved to at least Grade 1 or baseline, whichever is longer or until no further improvement can be expected.

7.2.2. Discontinuation From the Study

Reasons for discontinuation of a subject from the study include:

- Completed 15 years of follow up after the last T cell infusion
- Death
- Unable/unwilling to comply with study requirements
- Withdrawal of consent
- Investigator decision
- AE
- Lost to follow-up
- Pregnancy
- Termination of the study by the Sponsor

7.3. Consideration for Temporary Suspension of Enrollment

In addition to the periodic safety reviews by the SRC (Section 6.4.4), additional safety review will be undertaken by the Sponsor. Based on the severity of the AEs, the degree of T cell expansion, indicators of potential antitumor activity, and other factors, final decisions to halt or modify the study will be made by Adaptimmune's Safety Governance Board.

Furthermore, temporary suspension of enrollment and dosing will take place until the situation can be assessed by Adaptimmune's Safety Governance Board if:

- Any death occurs that is deemed to be at least possibly related to the ADP-A2M4CD8 product by the Investigator and the Sponsor; or
- Two or more Grade 4 autoimmune events deemed probably or definitely related to the ADP-A2M4CD8 product by the Investigator and the Sponsor; or
- A subject has positive replication competent lentivirus (RCL):
  - Confirmed positive peripheral blood mononuclear cell (PBMC) RCL and no other vector lot is available (refer to Section 7.3 and Figure 1, Section 10.6.2).
  - Positive biological RCL - all ADP-A2M4CD8 infusions are halted (refer to Section 7.3 and Figure 1, Section 10.6.2).

Following assessment by Adaptimmune's Safety Governance Board, enrollment and dosing may resume if agreed upon by the Sponsor and Investigators, and Regulatory Authorities.

7.4. Lost to Follow up

In cases where the subject is deemed 'lost to follow-up', the Investigator or designee must make every effort to regain contact with the subject; e.g., 3 documented attempts, one of which must be a certified letter to the subject's last known mailing address or local equivalent methods. These contact attempts should be documented in the subject's medical records. Should the subject continue to be unreachable, only then will he/she be considered to have withdrawn from the study with the primary reason as 'Lost to Follow-up'.

8. STUDY ASSESSMENTS AND PROCEDURES

The Time and Events are provided in Table 1 (Section 1.3.1) for the Interventional Phase of the study and in Table 2 (Section 1.3.2) for LTFU.

Subjects will have been assigned a unique subject identification number upon signing the ICF for the Screening Protocol (ADP-0000-001). The number assigned will serve as the same subject ID upon qualification and enrollment into the Interventional Phase of this study.

NOTE**:** A subject will have the same Subject ID in the Screening Protocol (ADP-0000-001) and in this study (ADP-0055-001). Refer to the Screening Protocol Study Procedures Manual for further details on assignment of Subject ID.

8.1. Background Assessments

8.1.1. Demographics

Demographic data including year of birth, age, sex, race and ethnicity will be collected at Screening.

8.1.2. Disease History

The following information will be included for disease history: primary tumor type, date of initial diagnosis, stage at initial diagnosis, type of histology, histological grade, results of any historical molecular testing performed (if available), and date of diagnosis of locally advanced, unresectable, or metastatic disease.

The status/expression levels of the following will be documented at Screening for each specific cancer type, if available:

- PD-L1 (all cancers)
- BRAF (melanoma and NSCLC)
- BRCA, somatic or germ line or methylation status (ovarian cancer)
- HER2 by either IHC or FISH (esophageal, EGJ, or gastric cancers)
- MSI or dMMR (esophageal, EGJ, or gastric cancers)
- EGFR (NSCLC)
- ALK (NSCLC)
- ROS1 (NSCLC)
- HPV or p16 (head and neck cancer)

8.2. HLA and MAGE-A4 Tumor Antigen Testing

Subjects who are identified by the Investigator as possible candidates for the trial must have completed screening under Screening Protocol (ADP-0000-001) to confirm that the subject has

the appropriate HLA alleles, i.e., is HLA-A*02 positive and have MAGE-A4 positive tumor prior to conducting the remaining study screening procedures.

HLA-genotyping at the allelic level (4-digit) will be conducted on a blood sample at a central reference laboratory using an FDA approved HLA Sequencing System for SBT of HLA. A central laboratory accredited by the American Society for Histocompatibility and Immunogenetics (ASHI) will review the results of HLA typing for inclusion and exclusion alleles and will adjudicate subject eligibility based on HLA results.

An archival tumor sample may be submitted for determination of MAGE-A4 expression, in which case the biopsy from the most current setting is preferred provided that there is sufficient tissue. If an archival specimen is unavailable, the subject must undergo a new biopsy. The subjects' tumor will be tested for MAGE-A4 antigen expression by IHC or by RNA expression using an analytically validated and CLIA-certified Clinical Trial Assay. Testing will be completed at a central laboratory contracted by the Sponsor.

Details regarding the collection and processing of the screening biopsy, sample requirements, and instructions for sample shipment to the central laboratory for MAGE-A4 IHC analysis are located in the Sample Collection Manual for protocol ADP-0000-001.

8.3. Efficacy Assessments

8.3.1. CT/MRI

Imaging scans of the chest, abdomen and pelvis should be performed at Screening (for patients who received bridging therapy), Baseline, Week 4, Week 8, Week 12, Week 16, and Week 24, and then every 3 months +/-1 month for 2 years and then every 6 months post-infusion or until disease progression and again at completion. The Week 4 scan may occur within +3 days but not before Week 4. Imaging scans should be performed at the time a subject withdraws from the study.

Lesion sites that have previously required radiotherapy should be recorded in the eCRF prior to lymphodepletion.

See Section 8.4.9 regarding brain magnetic resonance imaging (MRI) for safety assessment.

Acceptable imaging modalities for this study include:

- Diagnostic-quality computerized tomography (CT) scan with oral and/or IV iodinated contrast of the chest and abdomen/pelvis (CT is the preferred modality for tumor assessments)
- MRI of the abdomen/pelvis acquired before and after gadolinium contrast agent administration and if contrast enhanced CT is contraindicated for a subject, a non-contrast enhanced CT of the chest,
- MRI of the extremities, if clinically indicated.
- MRI of the brain acquired without and with contrast-enhancement (pre-and post-gadolinium chelate IV), (see Section 8.4.9).

- Digital photographs of skin lesions including a ruler for estimating the size of the lesion.

Once an imaging modality is chosen, that modality should be used throughout the study. To allow time for the immune response to become apparent and for potential transient inflammatory reaction of the disease to the treatment ("tumor inflammation"), response will not be assessed before 4 weeks post infusion of ADP-A2M4CD8, unless there is unequivocal clinical evidence of deterioration. Therefore, imaging scans should not be performed earlier than 4 weeks post infusion. Responses should be confirmed by repeat imaging scan performed not earlier than 4 weeks after the criteria for response was first met.

Investigators (in collaboration with a radiologist) will assess tumor response according to RECIST v1.1 for clinical decision making. Tumor measurements at site should be performed by the same Investigator or radiologist (to the extent that this is feasible).

Investigator assessment of response will guide patient care throughout the study.

8.3.2. Survival Data

Subject survival status is inferred from study visits until a date of death is reported. If a subject is unable to attend the site for visit (e.g., due to deteriorating condition or a change of location/country), the subject may be followed remotely to obtain survival information.

If a subject decides to withdraw from any further study assessments/procedures, the Investigator should ask if the subject is willing for survival data only to be collected, this discussion should be documented in the source notes.

If the subject cannot be contacted by the site, information available in public records e.g. obituaries may be used by the site to determine date of death, if appropriate, prior to withdrawing the subject from the study due to lost to follow-up.

8.4. Safety Assessments

Planned time points for all safety assessments are provided in the Main Time and Events table (Table 1) and the LTFU Time and Events Table (Table 2).

Additional tests may be done at any time if clinically indicated.

The Clinical Labs Section 10.2, Appendix 2 describes the assessments and parameters to be collected and recorded.

Screening visit assessments should be completed within 28 days of leukapheresis unless otherwise specified. Information regarding ECHO/MUGA scans, ECG and infectious disease assays performed as standard of care assessments within 4 weeks prior to Screening (prior to study consent) will be acceptable.

Baseline assessments must be conducted between 14 and 6 days prior to T cell infusion.

8.4.1. Medical History

Relevant medical history will be recorded at Screening in the subject's eCRF.

8.4.2. Physical Examination

Subjects will undergo a physical examination at Screening and Baseline. The frequency of physical examination at subsequent visits is specified in Table 1 and Table 2.

8.4.3. Prior Anticancer Therapies

Anticancer therapies include, but are not limited to, chemotherapy, antibodies, anticancer vaccines, cell therapies, radiation therapy, and surgical resections. On-study cancer surgeries and bridging therapies are to be recorded.

8.4.4. Prior and Concomitant Medications

Current medications and those for the previous 30 days are to be recorded on the concomitant medication page of the eCRF at Screening.

For LTFU assessments, this section is limited to new chemotherapies or other anticancer therapies (including mutagenic agents and other investigational agents).

8.4.5. ECOG

Performance status will be measured using the ECOG performance scale. See Section 10.8, Appendix 8 for guidance. It is recommended, where possible, that a subject's ECOG be assessed by the same person throughout the study. The frequency of the ECOG assessment is specified in Table 11.

8.4.6. Vital Sign

Measurement of vital signs (temperature, pulse, respirations and blood pressure) will be made at the frequency specified in Table 1.

On the day of T cell infusion (Day 1) vital signs should be measured pre-infusion, and at 5, 15, and 30 minutes, and 1, 1.5, 2, and 4 hours after the infusion has started.

8.4.7. Weight and Height

Height will be assessed at the Baseline visit. Weight is assessed at Screening, Baseline and other visits according to Table 1.

8.4.8. Cardiac and Pulmonary Assessments

Cardiac and pulmonary assessments will be performed locally at the site.

8.4.8.1. ECG

A single ECG is performed at Screening and at Baseline. Heart rate, rhythm, PR, RR, QRS and QTc intervals will be recorded.

For Screening, ECGs performed as standard of care within 4 weeks prior to the visit are acceptable.

8.4.8.2. ECHO/MUGA

An ECHO or MUGA scan will be performed at Screening to determine LVEF for eligibility. ECHO/MUGA scans performed as standard of care within 4 weeks prior to Screening are acceptable. Additional scans will only be performed if clinically indicated. NOTE: the same method of evaluation must be used consistently for any follow-up scans.

8.4.8.3. Telemetry

For subjects with known cardiac or pericardial tumor involvement at Baseline, inpatient telemetry monitoring should be carried out for a minimum of 7 days post- ADP-A2M4CD8 infusion.

8.4.8.4. Pulmonary Function Tests

Pulmonary function tests (PFTs) (FEV1 and DLCO) will be performed at Screening to determine eligibility. Additional PFTs will be performed only if clinically indicated.

8.4.9. Brain MRI

For subjects with melanoma or known brain metastases, an MRI of the brain with contrast should be obtained at Screening.

An MRI of the brain is required for all subjects at Baseline or within 1 month prior to lymphodepletion to rule out newly diagnosed, untreated brain metastases or to document stability of previously treated brain metastases. CT with IV contrast may be used only for subjects with contraindications to brain MRI.

If CNS metastases are documented at any point prior to lymphodepletion, then dedicated CT/MRI scans of CNS metastases should be performed at every on-study tumor assessment and included as non-target lesions in the tumor worksheet. If CNS metastases are not documented at Screening, then dedicated CNS CT/MRI scans should be performed as clinically indicated (refer to Section 5.3, exclusion criterion 7).

8.4.10. Lymphocyte subset (CD3, CD4, CD8)

Lymphocyte subset analysis including absolute count and percentage of CD3, CD4 and CD8 and CD4/CD8 ratio should be performed if locally available. Results are not required prior to leukapheresis.

8.4.11. Renal Function Assessment

Renal function (i.e., GFR) will be estimated or measured according to standard practice at the treating institution. Renal function will be reassessed at Baseline using the same methodology.

8.4.12. Hematology

Section 10.2, Appendix 2 describes the parameters to be collected and recorded

In Years 6 to 15, laboratory assessments are performed for as long as persistence is analyzed. If persistence samples are discontinued (Section 10.6.2) then laboratory assessments may be discontinued.

8.4.13. Clinical Chemistry

Section 10.2, Appendix 2 describes the parameters to be collected and recorded.

In Years 6 to 15, laboratory assessments are performed for as long as persistence is analyzed. If persistence samples are discontinued (Section 10.6.2) then laboratory assessments are discontinued.

8.4.14. Coagulation

Section 10.3, Appendix 3 describes the parameters to be collected and recorded.

8.4.15. Thyroid Function Tests

Section 10.3, Appendix 3 describes the parameters to be collected and recorded.

8.4.16. Hepatic Safety Assessments

For subjects who experience evidence of hepatic toxicity, increased hepatic monitoring criteria will apply to ensure subject safety and to enable evaluation of liver event etiology (Section 10.3.5, Appendix 3).

8.4.17. Pregnancy Test

Either serum or urine pregnancy test may be performed. Female subjects of childbearing potential (FCBP) must have a negative pregnancy test at Screening and prior to starting lymphodepleting chemotherapy.

8.4.18. Infectious Disease Screening

Testing for infectious disease markers is required only at Screening and does not need to be repeated at Baseline to satisfy the inclusion / exclusion criteria, unless more than 6 months has elapsed from Screening.

Subjects who are hepatitis B surface antigen negative but are hepatitis B core antibody positive must have undetectable hepatitis B DNA. Subjects who are HCV antibody positive will be screened for HCV RNA by any RT PCR or bDNA assay. Eligibility will be determined based on a negative Screening value.

Subjects who are seropositive for CMV at Screening require further surveillance (see Section 8.4.19).

Section 10.2, Appendix 2 describes the parameters to be collected and recorded.

8.4.19. CMV PCR

If subjects are CMV seropositive at Screening, CMV PCR assessments are needed at Baseline, on Day 1, Week 2, 4, 6, 8. See Section 10.4.3.3 for CMV prophylaxis and blood product screening if positive.

8.4.20. C-reactive Protein and Ferritin

In addition to the assessments shown in Table 1, if CRS is suspected, C-reactive protein (CRP) and ferritin levels should be measured approximately every other day until symptoms are improving or an alternative diagnosis is confirmed.

8.4.21. CARTOX 10

The CARTOX-10 neurological assessment should be performed from Day 1 (prior to T cell infusion) through Day 8 while the subject is hospitalized according to Table 1. The CARTOX-10 assessment may be discontinued once a subject is discharged from the hospital.

If a subject is thought to have ES, the CARTOX-10 should be used at least twice per day until resolution or stabilization. It can also be used at later visits if indicated. See Section 10.4.7, Table 9.

8.4.22. Persistence (Vector Copies)

Persistence of transduced T cells is also a major biomarker related to clinical response. Therefore, additional PBMC samples will be collected over the first 2 years following infusion (Section 8.6.5).

Samples are required for:

- Safety at Baseline, Week 24, Month 12 and then every 6 months until Year 5 and annually from Years 6 to 15.
    - If no gene modified cells are detected for three consecutive assessments and the subject is ≥5 years post-infusion (e.g., negative persistence assessments at Years 4, 4.5, and 5), no further monitoring of PBMCs is required for persistence and collection of samples may be discontinued (Section 10.6.2)
    - If at Month 12 or beyond post-infusion, greater than 1% PBMCs test positive for vector sequences, the subject's PBMCs will be evaluated for integration site analysis (Section 10.6.3).
- Research at Day 2, Day 4, Day 8, Week, 2, Week 4, Week 8, Week 12, Month 9, Month 15 and Month 21.

See Table 1 and Table 2.

Details on collection and shipment of blood sample for vector copies/persistence is described in the Laboratory Manual.

8.4.23. Replication Competent Lentivirus (VSV-G DNA)

RCL will be monitored using a PCR-based assay that detects and measures copies of the gene coding for the vector's envelope protein, namely VSV-G that is necessary for the assembly of pseudo typed infectious lentiviral particles but absent from the vector's backbone.

RCL testing will take place on subject's peripheral blood mononuclear cells (PBMCs) which are collected at Baseline and post infusion at Week 12, Week 24, Month 12, and then annually for 15 years. See Table 1 and Table 2 or scheduling.

If all samples are negative in Year 1, PBMC samples will be collected and archived annually until 15 years after the last T-cell infusion. Samples will be archived at Adaptimmune's centralized biorepository.

If a positive VSV-G DNA signal is obtained, the study Investigator will be informed, and the subject will be scheduled for a retest as soon as possible and no later than 1 month after the initial positive result was reported to the Sponsor. See Section 10.6.2 for additional information.

Details on collection and shipment of blood sample for RCL are described in the Laboratory Manual.

8.5. Adverse Events and Serious Adverse Events

8.5.1. Time Period for Collecting AE and SAE Information

AEs and SAEs will be collected as follows:

- From the date of signing the Interventional Informed Consent until the day before lymphodepletion starts, only SAEs related to study design/procedures (protocol mandated procedures, invasive tests, or change in existing therapy) or AEs leading to withdrawal from the study will be collected.
- All AEs and SAEs will be collected from the start of lymphodepletion until 12 months after administration of last IP. If a Subject proceeds to the LTFU phase prior to Week 12, all AEs would be collected at the Month 2 visit (see Section 1.3.2). After 12 months from last infusion, subjects will only be monitored for LTFU AEs as defined in Appendix 3, Section 10.3.6.
- During the LTFU phase, subjects will only be monitored for the emerging clinical conditions (LTFU AEs) defined in Appendix 3, Section 10.3.6.

All SAEs will be recorded on the SAE worksheet (SAEW) and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours after awareness of the event, as indicated in Appendix 3, Section 10.3.6.

SAE follow up information should be submitted on an updated SAEW within 24 hours if associated with a change in diagnosis and/or increased severity. Otherwise follow up should be submitted promptly within 7 days, and no later than within 30 days of receiving new information.

8.5.2. Methods of Detecting AEs and SAEs

The methods of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix 3, Section 10.3.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.5.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs and SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the subject is lost to follow-up (as defined in Section 7.4). Further information on follow-up procedures is given in Appendix 3, Section 10.3.3.

8.5.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the Investigator to the Sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/IECs, and investigators.
- Investigator safety reports are prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary. These safety reports are forwarded to Investigators in the form of Investigator Safety Letters (ISL).
- An Investigator who receives an ISL describing a SAE or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.
- On request of a competent authority in whose territory the clinical trial is being conducted, the Sponsor will submit detailed records of all AEs that are reported by the relevant Investigator(s).

8.5.5. Pregnancy

- Pregnancy (or pregnancy of a male subject's partner) is not considered an AE/SAE unless there is reason to believe the pregnancy may be the result of failure of the contraceptive being used due to interaction with the IP. Details of all pregnancies in female participants and female partners of male participants will be collected from the

start of lymphodepletion for as long as there is evidence of T cell persistence, or until the subject has confirmed disease progression.

- If a pregnancy is reported, the Investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 5. See Section 10.5.2 for guidance.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

The safety of ADP-A2M4CD8 during pregnancy and lactation has not been established in humans. The target antigen is known to be expressed on fetal germ line tissues and placenta, therefore female subjects who are pregnant, intending to become pregnant, or are breastfeeding are excluded from ADP-A2M4CD8 studies.

There is no preclinical or clinical trial data of ADP-A2M4CD8 in pregnant women; however, there is a reasonable but unproven likelihood that this intervention may be significantly embryotoxic or even an abortifacient given the underlying biology of the target. The effects on breast milk are unknown, therefore breastfeeding should be discontinued for the duration of the study, starting at the first dose of chemotherapy and for at least 12 months after receiving the IP, or 4 months after there is no evidence of persistence/gene modified cells in the subject's blood, whichever is longer.

The contraception guidelines provided in Section 10.5.1 should continue to be adhered to during LTFU.

A woman who becomes and remains pregnant during the study will be discontinued from the-Interventional Phase as exposure to radiation from imaging studies would be contraindicated. The subject would follow the LTFU Time and Events Table 2.

8.5.6. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

The following disease-related events (DREs) are common in participants and can be serious/life threatening:

- Progression of underlying malignancy and related symptoms

Because these events are typically associated with the disease under study, they will not be reported as an AE if they are clearly consistent with the suspected progression of the underlying cancer. Clinical symptoms of progression may be reported as AEs if the symptoms cannot be determined as exclusively due to progression of the underlying malignancy or does not fit the expected pattern of progression for the disease under study.

If there is any uncertainty about an AE being due only to the disease under study, it should be reported as an AE or SAE.

8.5.7. AEs of Special Interest

8.5.7.1. Cytokine Release Syndrome

Cytokine release syndrome (CRS) is a potentially life-threatening toxicity that has been observed following administration of antibodies and adoptive T cell therapies for cancer. It is defined clinically by symptoms that can mimic infection including pyrexia, nausea, diarrhea, headache, fatigue, tachycardia, hypotension, transaminitis, rash and dyspnea. Subjects should be assessed clinically for CRS at all visits according to Table 1. Most cases of CRS present within 7 days following cell infusion. It is important to evaluate the subject for concurrent infections. Potentially life-threatening complications of CRS include cardiac dysfunction, adult respiratory distress syndrome, neurologic toxicity, renal and/or hepatic failure and disseminated intravascular coagulation. CRS may also be associated with findings of macrophage activation syndrome or occur coincident with tumor lysis syndrome.

CRS is associated with rapid rise in serum cytokine levels under conditions of immune activation and although cytokines will be assayed serially throughout the study, results of the assays will not be available in real time; therefore, CRS should be graded and managed with supportive and immunosuppressive interventions according to the severity of symptoms [Lee, 2014].

The diagnosis of CRS is clinical and is supported by the exclusion of infection as well as the presence of increased cytokine levels and other biomarkers. CRS should be graded and managed with supportive measures and anti-IL-6 according to the severity of symptoms, see Section 10.4.6 for detailed guidance on management of CRS.

8.5.7.2. Encephalopathy Syndrome

Encephalopathy has been described in association with CAR-T therapy and termed CAR T cell related encephalopathy syndrome, or CRES [Neelapu, 2018]. CRES typically manifests as a toxic encephalopathy which is generally reversible. Early signs include diminished attention, language disturbance and impaired handwriting. Other signs/symptoms include confusion, disorientation, agitation, aphasia, somnolence, and tremors. In severe cases of CRES (defined as Grade >2), seizures, motor weakness, incontinence, mental obtundation, increased intracranial pressure, papilledema, and cerebral edema may also occur.

CRES occurring within the first 5 days after immunotherapy may be concurrent with high fever and cytokine release syndrome (CRS) symptoms. This form of CRES tends to be of shorter duration, lower grade (Grade 1 or 2, Table 8, Section 10.4.7) and is generally reversible with anti-IL-6 therapy. CRES presenting as delayed neurotoxicity with seizures or episodes of confusion can occur 3 or 4 weeks after CAR T‑cell therapy, after the initial fever and CRS subside.

Encephalopathy syndrome (ES) may occur with other cancer immunotherapies, including TCRs. Cancer patients may also be at risk for encephalopathic symptoms due to other causes ranging from mild to moderate somnolence and confusion as a result of sedating medications, to seizures in relation to brain metastases. The possible contribution of other medications, underlying disease and/or co-morbidities should be evaluated when considering a diagnosis of ES in relation to T cell therapy.

8.5.7.2.1. Monitoring for ES

Brain MRI (or CT Scan if MRI is not feasible) is recommended at the time of Screening and it is required at Baseline for all subjects. Baseline brain MRI should be repeated if more than 4 months have elapsed prior to lymphodepletion.

The CARTOX-10 is a neurological assessment tool that is used to assess cognitive function to monitor for ES (Section 10.4.7). The CARTOX-10 should be administered by a study physician. CARTOX-10 should be measured on the day of ADP-A2M4CD8 infusion prior to receiving treatment and through Day 8 while the subject is hospitalized. If the subject is discharged before Day 8 the CARTOX-10 may be discontinued according to the Time and Events Table (Table 1). Subjects with known brain metastases should be monitored at least twice per day for the first 5 days following ADP-A2M4CD8 infusion if hospitalized. If a subject is found to have ES, the CARTOX-10 should be used at every visit (at least twice per day if hospitalized) until resolution or stabilization. It can also be used at later visits if indicated. The CARTOX-10 forms part of the grading system for ES developed by Neelapu et al [Neelapu, 2018].

ES is graded and managed according to the severity of symptoms, see Section 10.4.7 for detailed guidance on grading and management of ES.

8.5.8. Long Term Follow Up Adverse Events

All subjects will be followed for 15 years from time of last T cell infusion for observation of delayed AEs in accordance with FDA and EMA requirements for gene therapy clinical trials [FDA, 2006b; FDA, 2010; EMA, 2009], see Table 2. These assessments will be collected in the Interventional Phase of the study until disease progression and thereafter in the LTFU phase. Reporting criteria for AEs related to gene therapy during LTFU are described in Section 10.3.6.

8.5.8.1. LTFU Letter to Primary Care Physician/Oncologist

A letter should be sent by the Investigator/study coordinator to the subject's primary care physician, local oncologist, or other physician that will notify him or her of this research study and will outline the features to look for and report as delayed AEs potentially related to this study (Section 10.6.4).

8.6. Biomarkers for Exploratory Objectives

[redacted]

[redacted]

[redacted]

- [redacted]
- [redacted]

9. STATISTICAL CONSIDERATIONS

The objectives and endpoints for this study are described in Section 3; this section focuses on key aspects of the analysis and reporting of the primary and secondary endpoints. Details for the analysis of all efficacy, safety, and exploratory endpoints will be provided in the Statistical Analysis Plan (SAP).

Intent-to-Treat (ITT) population: This is the population of all subjects who were enrolled in the trial. The ITT population will be used to assess the safety of the end-to-end autologous T cell therapy procedure.

Modified Intent-to-Treat (mITT) population: This is the population of all ITT subjects who received T cell infusion. The mITT population is the primary analysis population for safety and efficacy evaluations following T cell infusion.

9.1. Statistical Hypotheses and Sample Size Assumptions

The sample size of up to 30 subjects total at the selected dose group (inclusive of subjects accrued during the dose escalation) is based on clinical rationale described in Section 6.4.2; no formal hypothesis testing is planned.

Assessment of Adverse Event of Special Interests During Expansion Phase

Bayesian methods detailed below will be used to guide safety oversight by SRC as subjects are enrolled at the target dose range during the Expansion phase. The advantage of a Bayesian framework in this small study is that, in addition to being able to incorporate prior information, it also allows one to make evaluations without relying on large sample theory.

The rates of the following AESIs during the first or second infusion (see Section 8.5.7 for details) will be evaluated as subjects accrue in the Expansion phase:

- Grade ≥3 CRS
- Grade ≥3 ES

For each of these events (Grade ≥3 CRS or Grade ≥3 ES), the rate, p, is defined as the proportion of subjects who experience these events at any time during the study.

The strength of evidence that this rate, p, for example >0.15, if we were to proceed to enroll Nmax (=30) subjects will be quantified. For each of these events, the number of subjects with event, x, in n subjects (in the Expansion phase) is assumed to follow a binomial distribution, B(n, p). Assuming a fairly non-informative prior distribution, for example beta (0.1, 0.9) for p, the posterior distribution of p follows beta(0.1+x, 0.9+n-x) distribution. This then means that the future number of subjects with this event, Y in m =Nmax – n, follows a beta-binomial (m, 0.1+x, 0.9+n-x) distribution. Using the methods described by Lee [Lee, 2008] (with θ=0.5), the predictive probability that this rate exceeds 0.15 with Nmax subjects, will be computed as subjects accrue. This predictive probability may be assessed at a threshold of 0.50.

To illustrate this, assume that 6 subjects have been treated in the dose selected for Expansion phase. Subsequent Bayesian evaluation with be based on n=7. For values of n ≥7 and Nmax (=30), the predictive probabilities will be computed as x varies to a maximum of n. This

information along with number and percentage of subjects with each of these events will be provided to the SRC in order to support its review of safety data and benefit:risk considerations. See Table 5 below for illustration of when the predictive probability p >0.15, exceeds the threshold of 0.5.

Table 5: Number of Subjects with Event when Predictive Probability (p > 0.15 with Nmax=30 | x of n Subjects with Events) > 0.5

n (Number of Subjects)	*x (Subjects with Event)*	*Predictive Probability*
7	2	0.7984*
8	2	0.7414
9	2	0.6813
10	2	0.6194
11	2	0.5568
12	3	0.8503
13	3	0.8107
14	3	0.7664
15	3	0.7174
16	3	0.6643
17	3	0.6076
18	3	0.5478
19	4	0.866
20	4	0.8314
21	4	0.7905
22	4	0.7425
23	4	0.6867
24	4	0.6221
25	4	0.548
26	5	1
27	5	1
28	5	1
29	5	1
30	5	1

*For e.g., if 2 of 7 subjects experience any one event, then the predictive probability that this rate is >0.15 with 30 subjects exceeds 0.5 (i.e., is 0.7984)
Parameters for Beta prior distribution is 0.1 and 0.9
Reference: Lee (2008)

9.2. Statistical Analyses

Descriptive statistics will be provided for safety, laboratory, disposition, demographics and antitumor activity data. Bayesian predictive probabilities for AESI will be used to guide safety

oversight as subjects are enrolled at the target dose range during the Expansion phase (with first or second infusion).

Safety, demography, and disposition data will be summarized by each dose group and overall groups. Continuous data will include means, medians, standard deviations, and ranges, while categorical data will be summarized using frequency counts and percentages.

All AEs will be listed and coded by the Medical Dictionary for Regulatory Activities (MedDRA v21.0 or higher). The number and percent of subjects reporting any AEs will be tabulated by system organ class and preferred term and categorized by each dose group and overall group. AEs will be tabulated by toxicity grade, relationship to treatment and seriousness.

ORR will be summarized by two-sided 95% Wilson and Clopper Pearson confidence intervals (CI) in each dose group and across dose groups. As data permit, ORR may also be summarized by tumor type.

The endpoints BOR, TTR, DoR, DoSD, PFS, and OS will be summarized descriptively. Time to event endpoints will be listed and analyzed using Kaplan-Meier (K-M) methodology to estimate the median, and the 25th and 75th percentiles. OS will be assessed at fixed time points such as 1 year and 2 years, if applicable.

The SAP will provide full details about analyses for safety, efficacy and/or exploratory endpoints. This section captures key aspects of the analysis.

Subject disposition including number of subjects leukapheresed, lymphodepleted, and treated with ADP-A2M4CD8 will be summarized. Reasons for subject discontinuation from the study will be displayed.

9.2.1. Antitumor Activity Analyses

The primary analysis population for efficacy will be the mITT population. Secondary analyses may be conducted on the ITT, if it is different from the mITT population.

The ORR will be based on confirmed (tumor) responses per RECIST v1.1.

Sensitivity analyses of ORR will be based on Investigator assessment of overall response (per RECIST v1.1).

The ORR will be summarized using a two-sided exact Clopper-Pearson (exact binomial) 95% CI and two-sided 95% CI using the Wilson method.

The following secondary efficacy endpoints will be summarized:

- Best overall response (BoR) per RECIST v1.1
- Time to response, defined as the duration between the date of T cell infusion and the initial date of the response.
- Duration of response (DoR), defined as the duration from the initial date of the confirmed response to the date of PD based on RECIST v1.1 or death.
- Duration of stable disease (DoSD), defined as the duration from the date of T cell infusion to the date of disease progression based on RECIST v1.1.

- Progression-free survival (PFS), defined as the interval between the date of T cell infusion and the earliest date of disease progression based on RECIST v1.1 or death due to any cause.
- Overall survival (OS), defined as the duration between T cell infusion and death.

No hypothesis testing is planned for these secondary endpoints. Time to event endpoints (i.e., OS, DoSD and PFS) will be listed, summarized and displayed graphically using K-M methodology to estimate the median, and the 25th and 75th percentiles. Two-sided 95% CI will be produced. OS may be assessed at fixed time points such as 1 year and 2 years using K-M methods.

The following censoring rules will be applied:

- For DoSD, subjects who do not have a documented disease progression will be censored at the date of the last assessment.
- For OS, subjects who are lost to follow-up or still alive will be censored at the date of last contact.
- For PFS, subjects who do not have a documented date of disease progression or death will be censored at the date of the last study assessment.

The proportion of censored observations will be summarized.

For subjects receiving second infusion:

- ORR may be summarized (data permitting) using two-sided 95% CI based on Wilson and exact methods.
- Listing of the lesion data with derivations, such as BOR, visit overall response etc., based on RECIST v1.1 will be provided.

9.2.2. Safety Analyses

The primary analysis population for safety will be the mITT population. Safety will also be summarized for the ITT population if this is different from the mITT population.

The safety profile will be based on DLTs, AEs, SAEs, AESIs, RCL, LTFU AEs and T cell persistence. Other safety assessments will include vital signs measurements, and clinical laboratory test results.

These data will be summarized using appropriate descriptive statistics (i.e., continuous data will include means, medians, standard deviations, and ranges), while categorical data will be summarized using frequency counts and percentages.

In the Intervention Phase, AEs will be summarized using two time periods:

- From the time of signing the treatment ICF
- From start of lymphodepleting chemotherapy, defined as starting on the first day of lymphodepleting chemotherapy

AEs throughout the trial will be coded by MedDRA v 21.0 or higher. 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 toxicity grade, relationship to treatment and seriousness in tabulation. AE data will be summarized during the first infusion, the second infusion, and during the combined first and second infusion period.

LTFU AEs will be summarized and listed.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Data Handling and Record Keeping

10.1.1.1. Data Management

An Electronic Data Capture (EDC) system will be used to collect data pertaining to this trial. Trial data will be captured through an eCRF. Within the EDC system the eCRF data will be entered by the site staff and all source document verification and data cleaning will be performed by the Sponsor or designee (e.g., CRO).

The specifications for the EDC system will be documented and approved before the EDC system is released for live use. The validation of the eCRF data will be defined in a Data Management Plan. As data are entered into the eCRF, the validation checks will be performed and where necessary, queries will be raised. All queries raised will be held in the EDC database.

The EDC system is a validated software program that has been designed to comply with CFR21 Part 11 requirements. All users will access the system via a unique user name and password. A full audit history of all actions performed within the system is maintained. User accounts ensure that each user can only perform the tasks applicable to their role and only have access to the data applicable to their role.

Standard coding dictionaries, World Health Organization Drug and MedDRA will be used to code medications, medical history and AEs.

When all data have been entered and all data cleaning is complete the data will be locked and made available for analysis and reporting.

On completion of the study all eCRF data, including all associated queries and audit history, will be made available in PDF format to both the study Sponsor and the sites.

10.1.1.2. Case Report Forms

For each subject enrolled, the completed eCRF must be reviewed and signed by the PI or authorized delegate. If a subject withdraws from the study, the reason must be noted on the eCRF.

The Investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the Sponsor in the eCRFs and in all required reports.

10.1.1.3. Site Documentation and Source Data

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents are classified into two different categories: (1) Investigator Site File (ISF) and (2) subject specific source documents.

The Investigator is responsible for maintaining a complete and accurate ISF containing essential documents as required by ICH GCP.

Source documents contain the results of original observations and activities of a clinical investigation. Source documents include but are not limited to subject medical records/progress notes, appointment book, original laboratory reports, ECG printouts, CT/MRI scans, pathology and special assessment reports, and signed ICFs. In no circumstances is the eCRF to be considered as source data.

The Investigator must ensure the availability of source documents from which the information on the eCRF was derived.

The Investigator must permit authorized representatives of the Sponsor, the respective national, local or foreign regulatory authorities, the IRB/IEC and auditors to inspect facilities and to have direct access to the ISF and all source documents relevant to this study regardless of the type of media.

10.1.1.4. Data Retention and Availability

The Investigator must keep all essential study documents including source data on file for at least 25 years after completion or discontinuation of the Study. After that period of time the documents may be destroyed, subject to local regulations.

The Investigator will not dispose of any records relevant to this study without written permission from the Sponsor. If the Investigator cannot guarantee the archiving requirement at the investigational site for any or all of the documents, such study records may be transferred upon request to the Sponsor or its designee.

Should the Investigator wish to assign the study records to another party or move them to another location, the Sponsor must be notified in writing in advance.

Study documentation is subject to inspection by the Sponsor, its representatives and regulatory agencies and must be stored in such a way that it can be accessed/retrieved within a reasonable timeframe at a later date.

10.1.2. Study Monitoring

Study Monitoring will be conducted by the Sponsor or designated CRO.

It is understood the responsible monitor will contact and visit the Investigator regularly and will be allowed, on request, to inspect all records of the trial (e.g., eCRFs, ISF, and source documents) provided that subject confidentiality is maintained in accordance with local requirements.

It will be the monitor’s responsibility to inspect the eCRFs at regular intervals throughout the study, to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered. The monitor should have direct access to subject source documents to verify the entries on the eCRF. The Investigator (or designee) agrees to cooperate with the monitor (or designee) to ensure any discrepancies detected are resolved.

10.1.2.1. Audits and Inspections

The Sponsor or its representatives may conduct audits at investigative sites including, but not limited to, facilities where the study is being conducted, IP handling and accountability, presence of required documents, the informed consent process and comparison of eCRFs with source documents.

All study documentation including source data must be available for audit.

The Investigator agrees to cooperate fully with audits conducted at a convenient time in a reasonable manner.

Regulatory agencies may also inspect investigative sites during or after the study. The Investigator (or designee) should contact the Sponsor immediately if this occurs and provide copies of correspondence relating to requests for an inspection of the site facilities.

10.1.3. Regulatory and Ethical Considerations

10.1.3.1. Competent Authority Submissions

Adaptimmune or its authorized representatives will be responsible for ensuring that appropriate competent authority approvals are obtained according to local country requirements. Competent authority approval (or notification as applicable) will be obtained before initiation of the study.

10.1.3.2. Independent Ethics Committees

The final study protocol and subject informed consent documentation will be approved by the IRB/IEC and any other site level committee deemed appropriate by the Institution. Approval from each applicable committee will be received in writing before initiation of the study.

Protocol amendments must also be approved by the IRB/IEC (and other committees as applicable) before implementation, except in the case of changes made to protect subjects from immediate hazard, which may be implemented immediately.

10.1.3.3. Local Regulations/Declaration of Helsinki

The Investigator will ensure this study is conducted in full compliance with the principles of the "Declaration of Helsinki" or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study must fully adhere to the principles outlined in ICH GCP or with local law if it affords greater protection to the subject.

10.1.4. Informed Consent

It is the responsibility of the Investigator to obtain written informed consent from all study subjects prior to any study related procedures being performed. All consent documentation must be in accordance with applicable regulations and ICH GCP. Documentation must include the dated signature of both the subject (or the subject's parents or legally authorized representative as applicable) and the person conducting the consent discussion. If the subject is illiterate, an impartial witness should be present during the consent discussion, and the consent signed and

dated by the witness, the subject, and the person conducting the consent discussion. The ICF should be translated and communicated to the subject in a language that is understandable to the subject. Certified translations of the informed consent documentation will be provided as applicable.

A copy of the signed and dated informed consent should be provided to the subject before participation in the study.

Tests performed as standard of care prior to documentation of consent may be used for screening results as appropriate (Section 8.3).

10.1.5. Confidentiality

The confidentiality of records that may identify subjects will be protected in accordance with applicable laws, regulation and guidelines.

The Investigator must ensure that each subject's anonymity is maintained and protected from unauthorized parties. On eCRFs or other documents submitted to the Sponsor, subjects must not be identified by their names, but by a unique identification code allocated to them to ensure confidentiality on all study documentation. Subjects will retain this unique number throughout the study.

The Investigator will keep a subject enrollment log showing subject unique identification codes, names and addresses in the ISF.

The Sponsor and/or its representatives accessing subject records and data at site will take all reasonable precautions to maintain subject confidentiality.

10.1.6. Protocol Adherence

The Investigator must sign the protocol to confirm acceptance and willingness to comply with the study protocol.

The Investigator or designee will not deviate from the protocol unless necessary to eliminate an apparent immediate hazard to the safety, rights or welfare of any study subject. In the event of a protocol deviation for any reason, the Investigator will promptly report the deviation to the Sponsor in writing.

10.1.7. Study Suspension, Study Termination, and Study Completion

The Sponsor may suspend or terminate the study at any time for any reason. If the study is suspended or terminated the Sponsor will ensure applicable sites, regulatory agencies and IRBs/IECs are notified as appropriate.

If the Investigator stops/terminates the study at their site, the Sponsor must be notified. The Sponsor will ensure Regulatory Agencies and IRBs/IECs are notified as appropriate.

The Sponsor will ensure End of Study declarations are made to the relevant Regulatory Agencies/IECs in accordance with local regulations.

10.1.8. Public Posting of Study Information

The Sponsor is responsible for posting appropriate study information on applicable clinical study registry websites. Information included in clinical study registries may include participating Investigator's names and contact information.

10.1.9. Clinical Study Report

The results of the study will be presented in an integrated Clinical Study Report (CSR) according to ICH guideline E3: Structure and Content of Clinical Study Reports.

10.1.10. Publication Policy

The Investigator may not submit the results of the study for publication or present the results of the study without the prior written agreement of the Sponsor in accordance with the Clinical Trial Agreement. The results of this study will be published as a whole once all subjects have completed the study and the study results have been analyzed. Interim publications of data from the study may be made if mutually agreed between the Sponsor and the Investigators. Agreement will not be provided by the Sponsor where in the Sponsor's view interim publications would introduce bias or lead to any misrepresentation or inaccuracies in data.

Authorship will be determined in conformance with the International Committee of Medical Journal Editors (ICMJE) guidelines and/or publication guidelines if applicable.

10.1.11. Financial Disclosure

Investigators and sub-investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing updated information on financial interests during the course of the study and for 1 year after completion of the study.

10.2. Appendix 2: Clinical Laboratory Tests

Laboratory reference ranges for all tests conducted locally must be provided to the Sponsor before the study initiates.

Table 6: Protocol-Required Safety Laboratory Assessments

Hematology:	Red blood cell count (RBC) Hemoglobin (Hb) Hematocrit (HCT) Mean cell volume (MCV) Mean corpuscular hemoglobin (MCH) Mean corpuscular hemoglobin concentration (MCHC) Platelet count White blood cell count (WBC) with differential (absolute or percentage) • Neutrophils • Lymphocytes • Monocytes • Eosinophils • Basophils
Lymphocyte subset:	Absolute cell count or percentage of CD3, CD4, and CD8 (if locally available)
Clinical Chemistry:	Calcium Phosphorus Magnesium Albumin Bilirubin Alanine aminotransferase (ALT) Aspartate aminotransferase (AST) Alkaline phosphatase Lactate dehydrogenase (LDH) Sodium Potassium Bicarbonate/CO_2 Creatinine* Chloride Glucose BUN or Urea * 24 hr urine test or GFR
Other Tests:	Ferritin C-reactive protein

Coagulation Screen:	Prothrombin time (PT) *or* international normalized ratio (INR) Activated partial tissue thromboplastin time (aPTT)
Pregnancy Test:	Serum beta-HCG or urine test
Thyroid Function Test:	Thyroid stimulating hormone (TSH)
Infectious Disease:	HIV 1+2 antibody[#] Hepatitis B surface antigen Hepatitis B core antibody – if positive, test for HBV DNA Hepatitis C antibody – if positive, test for HCV RNA HTLV 1+2 IgG CMV IgG[#] Epstein Barr Virus (EBNA)[#] Treponema IgG or RPR [#] **Viral reactivation** CMV DNA PCR – peripheral blood for detection of reactivation. In the event of suspected end organ CMV disease, a biopsy may be required [#] Per Institutional Standard Practice is acceptable

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition

- An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) ≥ CTCAE Grade 3 or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (i.e., not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. A pre-existing condition is one that is present at the start of the study during Screening and is documented in the subject's medical history.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

A SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions.

- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

g. Additional protocol-defined criteria

- Any Grade ≥3 CRS
- Review any Grade 4 CTCAE lab value based solely on numerical criteria (e.g., white blood cells decreased) to determine whether it should be reported as a SAE.
- Hepatic events:
  - ALT ≥3xULN and bilirubin ≥2xULN (>35% direct bilirubin) OR
  - ALT ≥3xULN and international normalized ratio (INR) >1.5, if INR measured

10.3.3. Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- SAEs should be reported to the Sponsor or designate within 24 hours using the SAEW.
- The Investigator will then record all relevant AE/SAE information in the eCRF.
- It is **not** acceptable for the Investigator to send photocopies of the participant's medical records to Adaptimmune in lieu of completion of the SAEW/AE eCRF page.
- There may be instances when copies of medical records for certain cases are requested by Adaptimmune. Supporting documents such as pathology reports or imaging results can also be provided in conjunction with the SAEW. In these cases, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Adaptimmune.

- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

AEs will be graded according to the NCI CTCAE v 5.0. See Section 10.4.6 and Section 10.4.7 for guidance on grading of CRS, and ES, respectively. For AEs not specifically listed in the CTCAE, the Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Grade 1 - Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- Grade 2 - Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (ADL)[1].
- Grade 3 - Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL[2].
- Grade 4 - Life-threatening consequences; urgent intervention indicated.
- Grade 5 - Death related to AE.

An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

[1]Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
[2]Self care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not being bedridden.

Assessment of Causality

- The Investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The Investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

- There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial SAEW report to Adaptimmune. However, **it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAEW to Adaptimmune.**
- The Investigator will also assess the relationship between the lymphodepletion chemotherapy and each SAE.
- The Investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Adaptimmune to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide Adaptimmune with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed eCRF.
- SAE follow up information should be submitted on an updated SAEW within 24 hours if associated with a change in diagnosis and/or increased severity. Otherwise follow up should be submitted promptly within 7 days, and no later than 30 days of receiving new information.

10.3.4. Reporting of SAEs

SAE Reporting to Adaptimmune

- SAEs must be reported to Adaptimmune by completing the paper SAEW within 24 hours of the study personnel's discovery of the event.
- Complete the SAEW as fully as possible and obtain the Investigators signature. Create a PDF of the signed SAEW and submit to:
  - email Adaptimmune@primevigilance.com or
  - fax: 1-800-211-3460

- Do not delay reporting an SAE if the Investigator is unavailable to sign. Report the SAE as above and provide a copy of the signed SAEW as soon as possible afterwards.

The SAEW and additional information can be found in the Study Procedures Manual.

10.3.5. Hepatic Monitoring and Follow Up Assessments

Liver chemistry evaluation criteria are designed to assure participant safety and to enable evaluation of liver event etiology. Liver chemistries will be monitored in accordance with the Time and Events table (Table 1), and as clinically indicated.

If a Subject meets one of the criteria defined in Table 7, the specified actions and follow up assessments will be carried out.

Hepatic safety assessments will be included in this safety follow up.

Table 7: Hepatic Monitoring Criteria

Hepatic Monitoring Criteria	
ALT-absolute	ALT ≥8 × ULN
ALT Increase	ALT ≥5 × ULN but <8 × ULN persists for ≥2 weeks ALT ≥3 × ULN but <5 × ULN persists for ≥4 weeks
Bilirubin[1]	ALT ≥3 × ULN **and** bilirubin ≥2 × ULN (>35% direct bilirubin)
INR[1]	ALT ≥3 × ULN **and** international normalized ratio (INR) >1.5, if INR measured
Symptomatic[2]	ALT ≥3 × ULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity
Suggested Actions and Follow up Assessments	
Actions	**Follow Up Assessments**
• Complete the eCRF and a SAEW if the event meets the criteria for an SAE within 24 hours.[1] • Consider hepatologist consultation • Repeat liver chemistry tests (include ALT, AST, alkaline phosphatase and bilirubin) and INR. • Perform Follow-Up Assessments (See column to the right) • Monitor participants weekly with liver chemistry and INR until liver chemistry abnormalities resolve, stabilize, or return to baseline. For	• Viral hepatitis serology[3] • Serum CPK and LDH • CBC with differential to assess eosinophilia • PBMC blood sample for persistence[4] • Assess for the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity • Record use of concomitant medications (including acetaminophen, herbal remedies, and other over-the-counter medications) and alcohol use • **For bilirubin or INR criteria:** • Hepatologist consultation required

Hepatic Monitoring Criteria	
bilirubin or INR criteria, monitor participant twice weekly. • Fractionate bilirubin, if total bilirubin ≥2 × ULN.	• Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG) or gamma globulins. • Liver imaging (ultrasound, magnetic resonance, or computerized tomography) • Consider liver biopsy

1. All events of ALT ≥3 × ULN **and** bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT ≥3 × ULN **and** INR >1.5 may indicate severe liver injury **(possible 'Hy's Law') and must be reported as an SAE**. The INR stated threshold value will not apply to participants receiving anticoagulants.
2. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or hypersensitivity (such as fever, rash or eosinophilia).
3. Includes: Hepatitis A immunoglobulin M (IgM) antibody; HBsAg and HBcAb; hepatitis C RNA; cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, heterophile antibody or monospot testing); and hepatitis E IgM antibody.
4. Record the date/time of the PBMC blood sample draw on the eCRF. Instructions for sample handling and shipping are in the Laboratory Manual.

10.3.6. Reporting Criteria during Long Term Follow-Up (Years 1-15)

Due to the nature of the treatment, subjects are required to be followed for 15 years after the last treatment with genetically modified T cells according to FDA and EMA guidance [FDA, 2006a; FDA, 2010; EMA, 2009]. Subjects will be followed according to the schedule outlined in Section 1.3, Table 2. Emergence of any of the following new clinical conditions reported or observed and the action taken will be reported to the Sponsor:

- New Malignancies
- New incidence or exacerbation of a pre-existing neurological disorder
  - Excluding all Grade 1 neurologic AEs and Grade 2 AEs assessed as unrelated, unless the Investigator considers clinically significant
- New incidence or exacerbation of a prior rheumatologic or other autoimmune disorder
  - Excluding all Grade 1 autoimmune AEs and Grade 2 AEs assessed as unrelated, unless the Investigator considers clinically significant
  - All rheumatologic disorders will be reported irrespective of grade
- New incidence of a hematologic disorder
  - Excluding cytopenias following cytotoxic chemotherapy before bone marrow recovery
  - Excluding Grade 1 and 2 laboratory abnormalities, unless the Investigator considers clinically significant
- Opportunistic and/or serious infections
  - Excluding infections secondary to chemotherapy induced cytopenias

- Unanticipated illness or hospitalization deemed at least possibly related to gene modified cell therapy

These are the only AEs that will be collected during LTFU.

A detailed description of the event should include the date of diagnosis and the nature of the diagnosis. If the diagnosis is cancer, record the type and stage of the cancer. If the cancer is metastatic, list the metastatic sites. If a new malignancy is recorded in a vector target T cell type, tumor cells will be evaluated for vector sequences. If the tumor is positive for vector sequences or the surrogate sample is positive for vector sequences and is confirmed in accordance to this protocol, clonality analysis will be performed. If no evidence of oligo-or monoclonality is observed, a summary report of any and all analysis for the pattern of vector integration will be assembled and submitted within the annual report of the INDs listed on this protocol under which the subject(s) evaluated originally received their treatment. If evidence of oligo- or monoclonality is observed, an information amendment will be submitted within 30 days to the INDs listed on this protocol under which the subject(s) evaluated originally received their treatment.

Unexpected serious LTFU adverse reactions deemed at least possibly related to the gene modified cells (i.e., SUSARs) will be reported to the Regulatory Agencies and shared with Investigators as necessary in the form of Investigator Safety Letters (ISL).

10.3.7. Request for Autopsy for Death Following Administration of Gene Transfer Agents

In accordance with FDA and EMA guidance [FDA, 2006b; EMA, 2009], all subjects enrolled in this trial are asked to consider an autopsy and autopsies will be requested of the families for all subjects who die during participation in studies after administration of gene transfer agents.

Guidelines for autopsy tissue/sample collection, preparation and shipping are provided in the SAE and Autopsy Tissue Collection Kit Manual.

10.4. Appendix 4: Supportive Care Guidance

It is recommended that a specialist with experience in the administration of hematopoietic stem cell transplant and/ or other cell and gene therapy be involved in the care of study subjects. All subjects should be hospitalized for the T-cell infusion and for 72 hours following dosing to allow for close monitoring of post-infusion AEs. Staff treating trial subjects should be experienced in acute post-transplant care and the management of associated toxicities (e.g., cytopenias, CRS, ES).

Subjects are at risk for the development of certain adverse effects for which recommended management strategies have been developed. Adverse effects are most likely to occur within the first month following T-cell infusion but may occur at later time points.

Supportive care treatments recommended herein, including tocilizumab will be supplied by the pharmacy of the participating institution.

10.4.1. Lymphodepleting Chemotherapy Symptom Management

Cyclophosphamide and fludarabine are used as pre-conditioning lymphodepleting chemotherapy in this study. Symptoms associated with the use of cyclophosphamide and fludarabine are included in the respective product labels. Refer to the most current product labels.

10.4.1.1. Management of Neutropenia

The pre-conditioning chemotherapy is intended to cause lymphodepletion. However, neutropenia is also common. Prophylactic use of G-CSF is recommended in all subjects. G-CSF (i.e., filgrastim) should be used for management of neutropenia according to ASCO guidelines [Smith, 2015]. G-CSF should be given on Day 3 after the T-cell infusion until resolution of neutropenia (reaching an ANC of at least 2×10^9/L to 3×10^9/L or as per institutional practice).

Long-acting (pegylated) G-CSF may be given in preference to short acting daily G-CSF in accordance with institutional standard practice. Pegylated G-CSF will be given as one dose on Day 3 post-infusion of cellular therapy.

10.4.2. T-Cell Infusion Symptom Management

Mild transient symptoms have been observed following infusion of engineered T cells. The management of these symptoms is suggested but should not necessarily be confined to the below.

- Fever, chills, headache and temperature elevations will be managed with acetaminophen. It is recommended all subjects who develop fever or chills have a blood culture drawn.
- Nausea and vomiting may be treated with a non-steroidal anti-emetic of choice.
- Hypotension will initially be managed by IV fluid administration and further measures as dictated by standard medical practice.
- Hypoxemia will initially be managed with supplemental oxygen and further measures as dictated by standard medical practice.

10.4.3. Infection

Additional measures to treat and prevent infection are outlined below. In particular, fever and neutropenia should be aggressively managed as well as preemptive influenza therapy and other standard therapies for immunocompromised hosts, in accordance with institutional guidelines.

10.4.3.1. Pneumocystis jiroveci Pneumonia

Subjects should receive prophylaxis against Pneumocystis jiroveci pneumonia with drug, dose and duration according to institutional guidelines. Single strength trimethoprim sulfamethoxazole daily is the recommended first line agent, starting at day 28 post T-cell infusion for one year. Other regimens including atovaquone (1500 mg daily with food) or IV pentamidine (300 mg every four weeks) are also acceptable in cases of sulfonamide allergy or sulfa intolerance, Treatment should follow Institutional standards for autologous bone marrow transplants.

10.4.3.2. Herpes simplex and Varicella zoster

All subjects should receive prophylaxis with acyclovir (800 mg twice daily) or valacyclovir (500mg twice daily) for one year, or in accordance with institutional guidelines. In general, prophylaxis should start on day of T-cell infusion, or on day of lymphodepletion if the subject has a history of shingles or multiple HSV episodes.

10.4.3.3. Cytomegalovirus

Subjects will be screened for cytomegalovirus (CMV) seropositivity at study entry. If CMV viremia is detected at baseline, treatment should be initiated and evidence of viral clearance obtained, prior to lymphodepletion chemotherapy. All CMV seropositive subjects will continue to be monitored for CMV viremia by CMV DNA PCR as in Table 1 until 60 days post-infusion of ADP-A2M4CD8. In the event CMV viremia is observed an Infectious Diseases specialist should be consulted and treatment initiated if necessary, according to institutional practice. Recommended regimens include ganciclovir based therapy if ANC ≥1000, and foscarnet if ANC <1000.

If a subject experiences prolonged or secondary pancytopenia or lymphopenia additional monitoring for viral reactivation should be considered and treatment for viral infection initiated if necessary. A strategy for management of pancytopenia or bone marrow failure is described in Section 10.4.8.

10.4.3.4. Hepatitis B Prophylaxis

Subjects will be screened for HBV at study entry. Subjects who are hepatitis B core antibody positive must receive prophylaxis against viral reactivation using institutional protocols. Prophylaxis should be initiated prior to lymphodepleting therapy and continued for 6 months. Acceptable regimens include lamivudine (300 mg daily), entecavir (0.5 mg daily), or tenofovir (300 mg daily).

10.4.3.5. Syphilis

Subjects will be screened for syphilis at study entry in accordance with institutional standards. Subjects with positive screening results should be evaluated by an infectious diseases consultant. If determined to have syphilis infection, the subject should be treated before lymphodepletion chemotherapy.

10.4.3.6. Other Antimicrobial Prophylaxis

Antibacterial and antifungal prophylaxis should follow institutional standards for autologous bone marrow transplants.

10.4.4. Hematologic and Blood Product Support

Blood product support should be provided to maintain platelets > 10×10^9/L, Hb > 8.0 g/dL (or in accordance with institutional practice) and as clinically indicated. See AABB Guideline on platelet transfusion [Kaufman, 2015].

10.4.4.1. Irradiated Blood Product

Blood products transfused during the following study periods must be irradiated:

- within 4 weeks prior to leukapheresis (NOTE: leukapheresis should not be delayed for transfusions received prior to enrollment),
- within 4 weeks prior to initiation of lymphodepleting chemotherapy, and
- following lymphodepleting chemotherapy until at least 6 months following T-cell infusion or until lymphocyte count returns to $\geq 1.0 \times 10^9$/L (whichever is longer).

In addition, if a subject requires treatment with systemic steroids or immunosuppression, irradiated blood products must be given until recovery of immune function.

10.4.4.2. CMV Screened Blood Products

Subjects will be screened for CMV seropositivity on study entry. In order to reduce the risk of primary CMV infection all subjects (i.e., both CMV-positive and -negative subjects) should receive leukoreduced blood products where possible (excluding the IP infusion). Where leukoreduced blood is not available, CMV negative subjects must only receive blood products from CMV-seronegative donors from study entry to study completion including during LTFU.

10.4.5. Management of Autoimmunity

Subjects should be monitored throughout the trial for potential autoimmune reactions in response to the genetically engineered T cells that could include skin toxicity, liver toxicity, colitis, eye toxicity etc. If autoimmunity is suspected, the PI should be contacted, and every attempt should be made to biopsy the affected organ to clarify whether the symptoms are related to the ADP-A2M4CD8 therapy. If the subject sustains persistent Grade 2, or Grade 3 or 4 autoimmunity, consideration should be given to administration of corticosteroid therapy, either topically (e.g., skin, eyes) or systemically as clinically indicated.

10.4.6. Management of Cytokine Release Syndrome

Table 8 provides the recommended management of CRS according to grade, which has been further adapted from CTCAE for use with immunotherapy and should be implemented in accordance with institutional guidelines. Symptoms can mimic those seen with infection. The diagnosis of CRS is clinical and is supported by the exclusion of infection as well as the presence of increased cytokine levels and other biomarkers. Assessment and treatment guidelines are provided below. If CRS is suspected, in addition to assessment for infection, cytokine levels as described in Section 8.5.7.1 as well as CRP levels should be measured approximately every other day until symptoms are improving or an alternative diagnosis is confirmed.

Table 8: Management Guidelines for Cytokine Release Syndrome

Grade	Clinical Presentation for Grading Assessment	Management Guidelines
1	Constitutional symptoms not life-threatening (e.g., fever, nausea, fatigue, headache, myalgias, malaise)	• Vigilant supportive care[1] • Assess for infection and treat[2]
2	Symptoms require and respond to moderate intervention (Hypotension responds to fluids or one low dose pressor, hypoxia responds to <40% O_2.	• Monitor cardiac and other organ function • Vigilant supportive care[1] • Assess for infection and treat[2] • Treat hypotension with fluid and pressors. • Administer O_2 for hypoxia. • Administer anti-IL-6 therapy[3] (tocilizumab 8 mg/kg[4] IV or siltuximab 11 mg/kg IV) in subjects with extensive co-morbidities or of older age.
3	Symptoms require and respond to aggressive intervention hypotension requires multiple pressors or high dose pressors hypoxia requires ≥40% O_2, Grade 3 organ toxicity or Grade 4 transaminitis	• Monitor subject very closely for cardiac and other organ dysfunction. Most likely will require monitoring in an intensive care unit (ICU). • Vigilant supportive care[1] • Assess for infection and treat[2] • Treat hypotension with fluid and pressors. • Administer O_2 for hypoxia. • Administer anti-IL-6 therapy[3]

Grade	Clinical Presentation for Grading Assessment	Management Guidelines
4	Life-threatening symptoms Grade 4 organ toxicity (excluding transaminitis)	• Manage subject in ICU • Intensive supportive care including mechanical ventilation, fluids, pressors, antibiotics and other measures as required • Administer anti-IL-6 therapy[3]
5	Death	

1. Supportive care includes: monitor fluid balance, maintain adequate hydration and blood pressure
2. Assessment and treatment to include history and physical, blood and urine cultures, imaging studies, administration of antimicrobial agents for concurrent bacterial infections, and for treatment of fever and neutropenia as per institutional practice; and antipyretics, analgesics as needed.
3. For subjects requiring intervention beyond supportive measures, anti-IL-6 therapy should be the first line treatment (tocilizumab 8 mg/kg* IV or siltuximab 11 mg/kg IV).
4. The maximum dose for tocilizumab is 800 mg per dose. Corticosteroids can be used for subject's refractory to anti IL-6 therapy. Other immunosuppressor agents may also be used, including TNFα and IL-1R inhibitors

Source: Lee, 2014; Neelapu, 2018

For subjects requiring immunosuppressive intervention anti-IL-6 therapy should be the first line treatment. Tocilizumab is a humanized anti-IL-6 receptor antibody that has been approved for the treatment of CRS. Anecdotally, tocilizumab has produced rapid and complete correction of CRS with single doses [Maude, 2014]. The United States product insert (USPI) and Canadian Product Monograph for tocilizumab recommends a dose of 4-8 mg/kg administered over 1 hour in adult subjects as the first-line treatment of severe CRS. Subjects may receive a repeat dose(s) if clinical signs and symptoms do not improve at least 8 hours apart. For subjects with neurologic symptoms refractory to an initial dose of anti-IL-6 therapy, consider siltuximab for the second dose based on its mechanism of action directly against IL-6. Refer to Section 10.4.7 below for subjects experiencing encephalopathy concurrent with CRS.

Subjects unresponsive to anti-IL-6 therapy may require treatment with steroids. Lee [Lee, 2014] recommend steroids as second-line therapy for CRS as the response to anti-IL-6 therapy may be more rapid and owing to the potential of steroids to attenuate the antitumor effects of the adoptive T cell therapy. However, in subjects with Grade 3 or 4 CRS associated with neurologic dysfunction without significant hemodynamic instability or other life-threatening symptomatology, consideration may be given to the use of corticosteroids as immunosuppressive therapy. High doses (e.g., 2 mg/kg/day prednisone equivalent) may be required.

If CRS is suspected, a physician with expertise in the management of subjects following bone marrow transplant should be consulted. If high dose corticosteroids are required, treatment

should generally be continued until resolution to Grade 1 followed by tapering doses over several weeks.

Please review the most recent versions of the product labels for tocilizumab and siltuximab.

10.4.7. Grading and Management of Encephalopathy Syndrome (ES)

10.4.7.1. Grading of Encephalopathy Syndrome

Neelapu, et al [Neelapu, 2018] have developed a grading system for ES which incorporates the CARTOX 10‑point neurological assessment (CARTOX‑10) tool (Table 9). Points are assigned for each of the tasks in Table 9 which are performed correctly. Normal cognitive function is defined by an overall score of 10. The CARTOX-10 should be used to monitor all subjects for ES.

The CARTOX-10 assessment used for grading ES is presented in Table 9.

Table 9: CARTOX 10‑Point Neurological Assessment (CARTOX-10)

Task	CARTOX Points
Orientation to: year, month, city, hospital, and President/Prime Minister of country of residence	Total of 5 points (1 point for each)
Name three objects, for example point to: clock, pen, button	Total of 3 points (1 point for each)
Write a standard sentence, e.g., '*There are seven days in a week*'	1 point
Count backwards from 100 in tens	1 point

The CARTOX-10 score is used in grading of ES as presented in Table 10.

Table 10: Grading of Encephalopathy Syndrome (ES) [based on Neelapu, 2018]

Symptom or Sign	Grade 1	Grade 2	Grade 3	Grade 4
Neurological assessment score (by CARTOX-10[1])	7–9 (mild impairment) if different from baseline	3–6 (moderate impairment)	0–2 (severe impairment)	Patient in critical condition, and/or obtunded and cannot perform assessment of tasks
Raised intracranial pressure	NA	NA	Stage 1–2 papilledema[2], or CSF opening pressure <20 mmHg	Stage 3–5 papilledema[3], or CSF opening pressure ≥20 mmHg, or cerebral edema

Symptom or Sign	Grade 1	Grade 2	Grade 3	Grade 4
Seizures or motor weakness	NA	NA	Partial seizure, or non-convulsive seizures on EEG with response to benzodiazepine	Generalized seizures, or convulsive or non-convulsive status epilepticus, or new motor weakness

[1] See Table 8 for CARTOX‑10.
[2] Papilledema grading is performed according to the modified Frisén scale.
Source: Neelapu, 2018

10.4.7.2. Management of Encephalopathy Syndrome

The recommended management of ES should be based on toxicity grade. Table 11 provides guidance on the management of ES and should be implemented in accordance with institutional guidelines.

Grade 1 ES is primarily managed with supportive care as outlined below. For subjects requiring intervention beyond supportive measures, anti-IL-6 therapy should be the first line treatment of for ES in the setting of CRS (See Section 10.4.6 for CRS diagnosis and treatment guidelines). In the setting of concurrent CRS, for Grades 1-3 ES additional doses of anti-IL-6 therapy should be considered before instituting corticosteroids since the use of systemic steroids may abrogate the effects of the T cell therapy. For subjects with neurologic symptoms refractory to an initial dose of anti-IL-6 therapy, consider siltuximab for the second dose based on its mechanism of action directly against IL-6.

A neurology consultation should be obtained for subjects with ES for thorough neurological evaluation, and recommendations for further testing such as EEG and neuroimaging as indicated.

Table 11: Management of Encephalopathy Syndrome

Grade	Treatment
1	For all patients: • Vigilant supportive care; aspiration precautions; IV hydration • Withhold oral intake of food, medicines, and fluids, and assess swallowing • Convert all oral medications and/or nutrition to IV or enteral tube if swallowing is impaired • Avoid medications that cause central nervous system depression • Evaluate for other contributing causes and treat accordingly Unless symptoms are mild and transient (e.g., 1-point change in CARTOX-10 for less than 12 hours): • Neurology consultation including funduscopic exam to assess for papilledema • MRI of the brain with and without contrast (CT scan of the brain if MRI is not feasible). Further testing if indicated such as diagnostic lumbar puncture with measurement of opening pressure if increased intracranial pressure is suspected, or MRI spine if the subject has focal peripheral neurological deficits • Institute levetiracetam therapy and consider EEG if seizure activity is suspected • Consider anti-IL-6 therapy with tocilizumab 8 mg/kg[1] IV or siltuximab 11 mg/kg IV, if Grade 1 persists beyond 24 hours, or worsening and associated with concurrent CRS
2	• Supportive care and neurological work-up as described for Grade 1 ES • Anti-IL-6 therapy if associated with concurrent CRS • If refractory to anti-IL6 therapy or no evidence of CRS consider Dexamethasone 10 mg IV every 6 h or methylprednisolone 1 mg/kg IV every 12 h; Once initiated continue corticosteroids until improvement to Grade 1 ES and then taper • Consider transferring patient to intensive-care unit (ICU) if ES associated with Grade ≥2 CRS
3	• Supportive care and neurological work-up as indicated for Grade 1 ES • ICU transfer is recommended • Anti-IL-6 therapy if associated with concurrent CRS if not administered previously • Corticosteroids as outlined for Grade 2 ES if symptoms worsen despite anti-IL-6 therapy, or for ES without concurrent CRS; continue corticosteroids until improvement to Grade 1 ES and then taper • Stage 1 or 2 papilledema with cerebrospinal fluid (CSF) opening pressure <20 mmHg should be treated with a corticosteroid regimen as per Grade 4 below. • Consider repeat neuroimaging (CT or MRI) every 2–3 days if patient has persistent Grade ≥3 ES

Grade	Treatment
4	• Supportive care and neurological work-up as indicated for Grade 1 ES • Consider neurosurgical consultation for patients with evidence of increased intracranial pressure • ICU monitoring; consider mechanical ventilation for airway protection • Anti-IL-6 therapy and repeat neuroimaging as described for Grade 3 ES • High-dose corticosteroids continued until improvement to Grade 1 ES and then taper; for example, methylprednisolone IV 1 g/day for 3 days, followed by rapid taper at 250 mg every 12 h for 2 days, 125 mg every 12 h for 2 days, and 60 mg every 12 h for 2 days

[1] Maximum amount of tocilizumab per dose is 800 mg

10.4.8. Management of Pancytopenia with Bone Marrow Failure / Aplastic Anemia

Pancytopenia with bone marrow failure / aplastic anemia was reported after initial bone marrow recovery from high-dose chemotherapy followed by infusion of adoptive T cell therapy [D'Angelo, 2017]. Bone marrow recovery following lymphodepletion will be defined as:

- Absolute neutrophil count ≥ 1,000/μL for 2 consecutive measurements approximately seven days apart, and
- Platelet count ≥ 20,000/μL without transfusion support for one week.

Aplastic anemia is a rare hematological disorder characterized by pancytopenia and a hypocellular marrow. Subjects are usually symptomatic on presentation, but some are detected incidentally when unexpected cytopenias are found on a routine blood count. Blood counts are collected according to Table 1. The diagnosis of severe aplastic anemia is made in the setting of a hypocellular bone marrow when 2 of the following 3 blood counts are met: absolute neutrophil count < 500/μL, absolute reticulocyte count < 60,000/μL, and platelet count < 20,000/μL, and myelodysplastic syndrome is ruled out. The clinical consequences of aplastic anemia are life-threatening bleeding from thrombocytopenia, and infection as a result of neutropenia. Bacterial and fungal infections are common and a significant cause of morbidity and mortality.

Management of bone marrow suppression and related cytopenias in aplastic anemia is challenging, with no clearly established guidelines regarding immunosuppression. Treatment is largely supportive, including transfusions and treatment of infections. If there is evidence of, or concern for the development of pancytopenia (decreasing hemoglobin, platelets or neutrophils, or increasing transfusion requirements) following initial bone marrow recovery the following measures should be implemented:

1. Consult a physician with expertise in the management of aplastic anemia
2. Increase the frequency of CBCs as clinically indicated.
3. Exclude other alternative etiologies such as other drugs, viral causes, etc.
4. An early bone marrow biopsy is recommended for clinical diagnosis, with a sample to be provided to the Sponsor for study. Details on tissue collections, kit use and shipment information can be found in the Sample Collection Manual.

5. A matched peripheral blood sample should be collected in parallel with the bone marrow sample and provided to the Sponsor.
6. Initiate treatment with G-CSF.
7. Consult an Infectious Diseases expert.
8. Once alternative etiologies have been excluded, strongly consider immunosuppression (e.g., methylprednisolone 2 mg/kg initial dose) or more aggressive regimens (e.g., antithymocyte globulin (ATG), cyclosporine, eltrombopag) as well as antimicrobial prophylaxis/therapy with the advice of your hematology/Infectious Diseases consultant(s). If high dose corticosteroids are initiated, continue for a minimum of 5 days and taper gradually with advice from expert consultants.

10.5. Appendix 5: Contraceptive Guidance and Collection of Pregnancy Information

Definitions:

Females of Childbearing Potential (FCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered FCBP

1. Premenarchal
2. Premenopausal female with 1 of the following:
    - Documented hysterectomy
    - Documented bilateral salpingectomy
    - Documented bilateral oophorectomy

    For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., mullerian agenesis, androgen insensitivity), Investigator discretion should be applied to determining study entry.

    NOTE: Documentation can come from the site personnel's: review of the participant's medical records, medical examination, or medical history interview.
3. Postmenopausal female
    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
        – A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence

of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.

- Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.5.1. Contraception Guidance:

Female and male subjects of reproductive potential must agree to avoid becoming pregnant or impregnating a partner, respectively. The required duration of contraception is described below:

- Female subjects of childbearing potential (FCBP) must agree to use an effective method of contraception starting at the first dose of chemotherapy for at least 12 months or 4 months after the gene modified cells are no longer detected in the blood, whichever is longer.
- Male subjects must be surgically sterile or agree to use a double barrier contraception method or abstain from heterosexual activity with a female of childbearing potential starting at the first dose of chemotherapy and for 4 months thereafter or longer (if indicated in the country specific monograph/label for cyclophosphamide).

Effective methods of contraception include: intra-uterine device, injectable hormonal contraception, oral contraception, or two adequate barrier methods (e.g., diaphragm with spermicide, cervical cap with spermicide, or female condom with spermicide - spermicides alone are not an adequate method of contraception).

Abstinence (relative to heterosexual activity) can be used as the sole method of contraception if it is consistently employed as the subject's preferred and usual lifestyle and if considered acceptable by local Regulatory Agencies and IRBs/IECs. Periodic abstinence (e.g., calendar, ovulation, sympto-thermal, post-ovulation methods, etc.) and withdrawal are not acceptable methods of contraception.

The contraception guidelines should continue to be followed during LTFU.

10.5.2. Collection of Pregnancy Information

10.5.2.1. Female Participants Who Become Pregnant

- The Investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a participant's pregnancy.
- The participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any

termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such. Any post-study pregnancy related SAE considered reasonably related to the study intervention by the Investigator will be reported to the Sponsor as described in Section 10.3.4. While the Investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will be discontinued from further efficacy assessments (exposure to radiation from imaging studies is contraindicated in pregnancy), and will follow the LTFU schedule.

10.5.2.2. Male Participants with Partners Who Become Pregnant

- The Investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive ADP-A2M4CD8.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

10.6. Appendix 6: Long Term Follow Up

10.6.1. Background to Safety Monitoring in LTFU

10.6.1.1. Monitoring and Management of Replication-Competent Lentivirus

Replication Competent Lentivirus (RCL) is a theoretical risk associated with the use of lentiviral vectors; no RCL has ever been detected in vitro or in vivo. The risk is derived from the detection of replication competent retrovirus (RCR) during the use of early γ retroviral vector packaging systems which were inadequately designed to avoid recombination events between the vector and packaging components [Miller, 1990]. RCR resulted in death due to the onset of lymphoma in 3 of 10 monkeys after receiving bone marrow cells transduced with an RCR contaminated vector lot [Donahue, 1992]. Updated γ retroviral packaging systems have not been associated with RCR, however as a result of the Donahue study, RCR/RCL must continue to be rigorously evaluated in vector and cell lots, and in subjects post infusion with any product involving a retrovirus [FDA, 2006a; EMA, 2009].

A RCL may be generated during the production phase or subsequently after introduction of vector transduced cells into the subject. RCL may be generated by homologous or non-homologous recombination between the transfer vector and packaging elements, or endogenous retroviral elements [Chong, 1998; Garrett, 2000]. A RCL resulting from the production phase of the lentivirus used in this trial is highly unlikely since elements are incorporated in the design of the vector system that minimize vector recombination and generation of RCL. Nevertheless, generation of an RCL by recombination with an endogenous virus (i.e., HIV) in the subject following infusion of the cell product remains a theoretical possibility. The consequences of such recombination events could be neutral, could reduce the replication rate or pathogenicity of the subject's endogenous virus, or could increase the replication rate or pathogenicity of the subject's endogenous virus. Since the development of a strain with increased pathogenicity would pose greater risk to both the subject and their close contact(s), periodic monitoring for RCL is conducted during the course of the trial and during the 15 year follow up.

10.6.1.2. Insertional Oncogenesis

Monitoring for insertional oncogenesis follows the recommendations set forth in the FDA and EMA guidance's [FDA, 2006a; FDA, 2006b; EMA, 2009]. Insertional oncogenesis is a theoretical risk in T cells transduced with a lentiviral vector. T cells appear resistant to transformation by integrating viruses [Cattoglio, 2010; Newrzela, 2008]. However, there are cases of oncogenesis with γ-retroviral transduced stem cells. Four of nine subjects with X-linked severe combined immunodeficiency (X-SCID) treated with retrovirus transduced stem cells were found to have insertion near the LMO2 proto-oncogene promoter, leading to aberrant transcription and expression of LMO2 which resulted in acute T cell lymphoblastic leukemia [Hacien-Bey-Abina, 2003; Hacien-Bey-Abina, 2014]. Additionally, two subjects treated for X-linked chronic granulomatous disease (X-CGD) with retroviral transduced stem cells demonstrated insertional activation of the EVI1 transcription factor which resulted in genetic instability, monosomy 7 and clonal progression toward myelodysplasia [Stein, 2010].

10.6.2. Testing for RCL and Persistence

RCL (VSV-G DNA) will be monitored using a PCR-based assay that detects and measures copies of the gene coding for the vector's envelope protein, namely VSV-G that is necessary for the assembly of pseudotyped infectious lentiviral particles but absent from the vector's backbone. The scheme for RCL testing is presented in Figure 1 below. RCL testing and monitoring will take place on subject's peripheral blood mononuclear cells (PBMCs) which will be collected at Baseline and then at 3, 6, and 12 months post-infusion and annually from year 2-15. Samples will be tested for the presence of VSV-G DNA copies.

If all samples are negative in year one, PBMC samples will be collected and archived annually until 15 years after the last T-cell infusion. Samples will be archived at the Sponsor's centralized biorepository.

If a positive VSV-G DNA signal is obtained, the study Investigator will be informed, and the subject will be scheduled for a retest as soon as possible and no later than one month after the initial positive result was reported to the Sponsor. A review by the SRC and the Sponsor's Safety Governance Board will take place.

Response to potential outcomes of second test:

- If the second test is negative, then subject samples will continue to be tested for VSV-G DNA copies until VSV-G DNA copies are not detected for 3 consecutive annual assessments as described in Figure 1, at which time the subject samples will be collected and archived annually until year 15.
- If the second test is positive, infusions for all subjects receiving T cells modified with the same vector lot will be postponed. The subject with the confirmed positive VSV-G signal will be scheduled for leukapheresis and a biological RCL test will be performed on the leukapheresis product. The biological RCL test assesses whether there is active production of infectious viral particles from the leukapheresis product [Manilla, 2005].

If the biological RCL test is positive, all infusions using the same T cell receptor in the interventional protocol(s) will be halted. An action plan will be discussed with FDA and other regulatory authorities and experts as appropriate. Additional subjects will not be treated with the same T cell receptor until such time as a plan is completed, reviewed, and agreed upon.

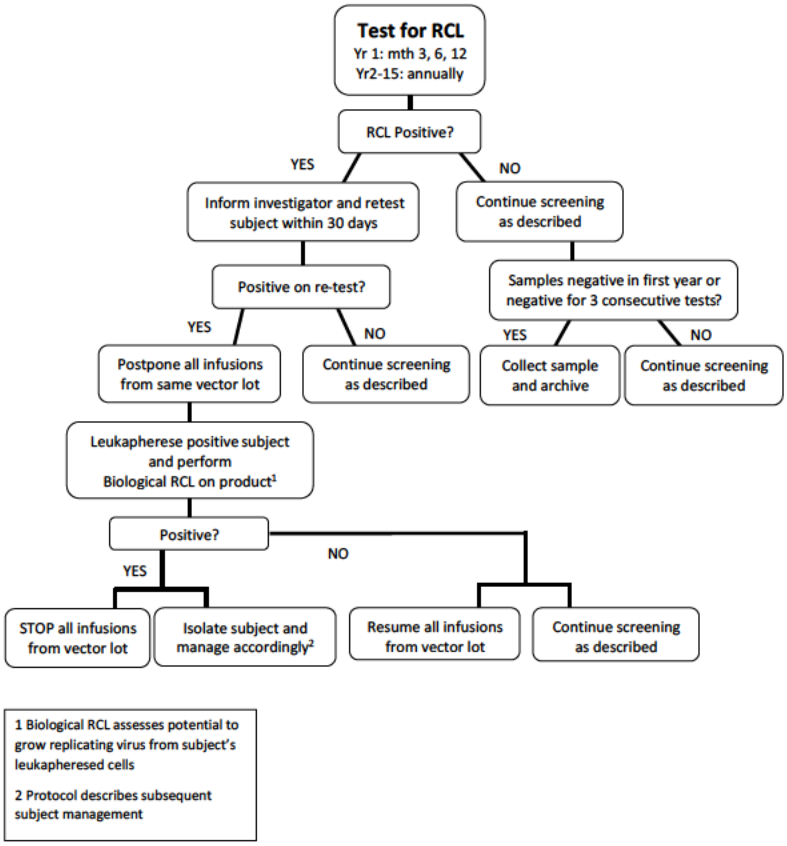
If the biological RCL test is negative, infusions for all subjects can resume.

Regulatory agencies and the gene therapy community have previously discussed measures to be taken should a biological RCL be confirmed in a subject [FDA, 2006a]. However, because the probability and characteristics of a RCL are unknown, no concrete plans have been put in place. As of the writing of this protocol, it is agreed the subject must be isolated and no additional subjects treated with the same T cell receptor therapy until a plan is agreed upon as outlined above.

The following approaches have been discussed for subject management:

1. Intensive follow up of subject in consultation with FDA, and other regulatory authorities, NIH, gene therapy experts, study investigators, and HIV physicians.
2. Provide targeted antiretroviral therapies based on genotyping of the RCL.

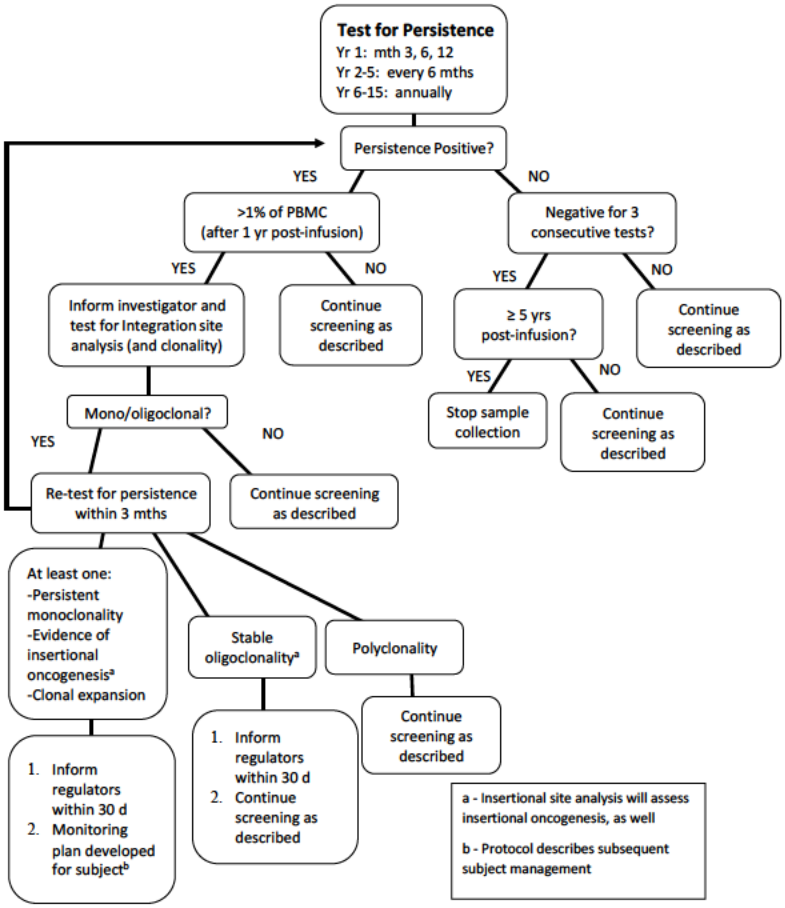
Figure 1: Flow Chart for Testing for Replication Competent Lentivirus (RCL)



PBMC samples will be collected and used as the "surrogate sample" for monitoring persistence of gene modified cells in subjects. Subject samples will be tested for persistence at Baseline, 6- and 12-months post-infusion and every 6 months for 5 years and annually from year 6-15 in accordance with the FDA and EMA guidance's [FDA, 2006a; FDA, 2006b; EMA, 2009]. The scheme for testing for persistence is presented in Figure 2.

The samples will be tested using a PCR-based method to detect the presence of the packaging signal sequence (Psi) which is part of the lentiviral vector used to transduce T cells. Detection of Psi DNA copies reflects persistence of the genetically modified T cells. If at 1 year or beyond post-infusion, greater than 1% PBMCs test positive for vector sequences, the subject's PBMCs will be evaluated for integration site analysis (Figure 2). If no gene modified cells are detected for three consecutive assessments and subject is ≥5 years post-infusion (for example, negative persistence assessments at year 4, 4.5 and 5), no further monitoring of PBMCs is required for persistence and collection of samples for persistence may be discontinued. NOTE: Samples for RCL must continue to be collected and archived annually for 15 years after the last T-cell infusion. Hematology and chemistry assessments may also be discontinued.

Figure 2: Flow Chart for Testing for Persistence



10.6.3. Integration Site Analysis

If persistence, as detected by the presence of vector sequences (Psi DNA copies), is present in >1% of PBMC at 1 year or beyond post-infusion, DNA from the subject's PBMCs will be sent for Next-Gen Sequencing for integration site analysis. Integration site analysis assesses clonality and the possibility of insertional oncogenesis.

Clonality is defined as follows: 1) monoclonality is 1 predominant clone at ≥5% of transduced T cells; 2) oligoclonality is defined as 2-5 predominant clones, each at ≥5% of transduced T cells; and 3) polyclonality is defined as no single predominant clone of ≥5% of transduced T cells.

If there is clonal dominance in the genetically modified T cell population (either monoclonality or oligoclonality) the persistence assessment will be repeated within 3 months on a new sample. If the repeated analyses demonstrates: 1) persistent monoclonality, 2) other evidence of insertional oncogenesis (for example, integration of the vector in the promoter region of a known oncogene or tumor suppressor gene), or 3) clonal expansion (an increase in percent predominance of a clone), there will be a review by the Safety Review Committee and the Sponsor's Safety Governance Board to develop a monitoring plan specific to the health care risk

and strategies to inform appropriate subjects, investigators, FDA and other regulators of the findings.

If the integration site analysis indicates polyclonality of the genetically modified T cell population then screening for persistence continues as scheduled (Table 2, Figure 2).

10.6.4. Letter to Physician - LTFU notification

[date]

[name and address]

Dear [physician name],

Your patient [patient name] has participated in a clinical research study, "A Phase 1 Dose Escalation Study To Assess Safety And Efficacy Of ADP-A2M4CD8 In HLA-A2+ Subjects With MAGE-A4 Positive Tumors (ADP-0055-001)", that requires 15-year monitoring for adverse events. To aid in reporting of adverse events that are possible related to the clinical research study, we are asking the patients on our research study to designate a primary care or infectious disease physician that may help in the monitoring and reporting of adverse events. Your patient has designated you. If upon any of your visits with your patient, any of the following events are reported or discovered, please contact the study nurse or physician as soon as possible:

- New Malignancies
- New incidence or exacerbation of a pre-existing neurological disorder
  - Excluding all Grade 1 neurologic AEs and Grade 2 AEs assessed as unrelated, unless the Investigator considers clinically significant
- New incidence or exacerbation of a prior rheumatologic or other autoimmune disorder
  - Excluding all Grade 1 autoimmune AEs and Grade 2 AEs assessed as unrelated, unless the Investigator considers clinically significant
  - All rheumatologic disorders will be reported irrespective of grade
- New incidence of a hematologic disorder
  - Excluding cytopenias following cytotoxic chemotherapy before bone marrow recovery
  - Excluding Grade 1 and 2 laboratory abnormalities, unless the Investigator considers clinically significant
- Opportunistic and/or serious infections
- Excluding infections secondary to chemotherapy induced cytopenias
- Unanticipated illness or hospitalization deemed at least possibly related to gene modified cell therapy

If your patient experiences any of these events, please refer them back to their study physician. Please contact the study coordinator below as soon as you can so that they can record the event and then monitor your patient's health if necessary. When you call, remember to mention the protocol number of the study which is ADP-0055-001, patient ID [XXX] and the study title

which is “A Phase 1 Dose Escalation Study To Assess Safety And Efficacy Of ADP-A2M4CD8 In HLA-A2+ Subjects With MAGE-A4 Positive Tumors (ADP-0055-001)”.

Study Physician:

Name: [Study physician name]

Phone: [Study physician phone]

Email: [Study physician e-mail]

Study Coordinator:

Name: [Study coordinator name]

Address: [Study coordinator address]

Phone: [Study coordinator phone]

Email: [Study coordinator e-mail]

If you have any questions about this letter or the study itself, please do not hesitate to contact the above study nurse or physician.

Thank you for your support in helping us to monitor for delayed adverse events.

Best regards,

[study physician/coordinator]

10.7. Appendix 7: Efficacy Reporting

10.7.1. RECIST 1.1 Criteria for Evaluating Response in Solid Tumors

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. CT is the best currently available and reproducible method to measure lesions selected for response assessment. MRI is also acceptable in certain situations (e.g., for body scans but not for lung). Ultrasound (US) should not be used to measure tumor lesions. The same modality should be used when comparing or making assessments.

Clinical lesions will only be considered measurable when they are superficial and ≥10 mm in diameter as assessed using calipers. For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a subject to be considered in complete response.

Cytology and histology can be used in rare cases (e.g., for evaluation of residual masses to differentiate between partial response and complete response or evaluation of new or enlarging effusions to differentiate between progressive disease and response/stable disease).

Use of endoscopy and laparoscopy is not advised. However, they can be used to confirm complete pathological response.

All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

Measurable lesions

Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm; when CT scans have slice thickness >5 mm, the minimum size should be twice the slice thickness).
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable).

Measurable lesions

- **Malignant lymph nodes** to be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness is recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.
- **Lytic bone lesions or mixed lytic-blastic lesions** with identifiable soft tissue components that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered measurable if the soft tissue component meets the definition of measurability described above.
- **'Cystic lesions'** thought to represent cystic metastases can be considered measurable if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same subject, these are preferred for selection as target lesions.

Non-measurable lesions

Non-measurable lesions are all other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with 10 to <15 mm short axis), as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

- **Blastic bone lesions** are non-measurable.
- **Lesions with prior local treatment**, such as those situated in a previously irradiated area or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

Target Lesions

- All measurable lesions up to a maximum of two lesions per organ and five lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline.
- Target lesions should be selected on the basis of their size (lesions with the longest diameter) and be representative of all involved organs, as well as their suitability for reproducible repeated measurements.
- All measurements should be recorded in metric notation using calipers if clinically assessed. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters, which will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease. If lymph nodes are to be included in the sum, only the short axis will contribute.

Non-target Lesions

All lesions (or sites of disease) not identified as target lesions, including pathological lymph nodes and all non-measurable lesions, should be identified as **non-target lesions** and be recorded at baseline. Measurements of these lesions are not required and they should be followed as 'present', 'absent' or in rare cases, 'unequivocal progression'.

Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (NOTE: the appearance of one or more new lesions is also considered progressions).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Special notes on the assessment of target lesions:

- Lymph nodes identified as target lesions should always have the actual short axis measurement recorded even if the nodes regress to below 10 mm on study. When lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if CR criteria are met since a normal lymph node is defined as having a short axis of <10 mm.
- Target lesions that become 'too small to measure'. While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small. However, sometimes lesions or

lymph nodes become so faint on a CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being 'too small to measure', in which case a default value of 5 mm should be assigned. Lesions that split or coalesce on treatment. When non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis)

NOTE: If tumor markers are initially above the upper normal limit, they must normalize for a subject to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Special notes on assessing progression of Non-Target lesions

Progressive Disease (PD): Unequivocal progression of existing non-target lesions.

- **When subject has measurable disease**. To achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status.
- **When subject has only non-measurable disease.** There is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified, a useful test that can be applied is to consider if the increase in overall disease burden based on change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease. Examples include an increase in a pleural effusion from 'trace' to 'large' or an increase in lymphangitic disease from localized to widespread.

New lesions

The appearance of new malignant lesions denotes disease progression:

- The finding of a new lesion should be unequivocal (i.e., not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor, especially when the subject's baseline lesions show partial or complete response).
- If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the scan where the lesion was first identified.
- A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and disease progression.

It is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

Negative FDG-PET at baseline, with a positive FDG-PET at follow-up - is PD based on a new lesion.

No FDG-PET at baseline and a positive FDG-PET at follow-up:

- If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.
- If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan).
- If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

Summary of the overall response status calculation at each time point:

Target Lesions	**Non-Target Lesions**	**New Lesions**	**Overall Response**	**Best Overall Response when Confirmation is Required**[1]
CR	CR	No	CR	≥4 weeks confirmation**
CR	Non-CR Non-PD	No	PR	≥4 weeks confirmation**
CR	Not evaluated	No	PR	

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required[1]
PR	Non-CR Non-PD Not evaluated	No	PR	
SD	Non-CR Non-PD Not evaluated	No	SD	Documented at least once ≥4 week. from Baseline**
Not all evaluated	Non-PD	No	NE	
PD	Any	Yes or No	PD	No prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript (Eisenhauer, 2009) for further details on what is evidence of a new lesion
** Only for non-randomized trials with response as primary endpoint
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression

Confirmation

In non-randomized trials where response is the primary endpoint, confirmation of PR and CR is required to ensure responses identified are not the result of measurement error. This will also permit appropriate interpretation of results in the context of historical data where response has traditionally required confirmation in such trials.

In the case of SD, measurements must have met the SD criteria at least once after study entry at a minimum interval (in general not less than 6–8 weeks) that is defined in the study protocol.

Missing Assessments and Inevaluable Designation

When no imaging/measurement is done at all at a particular time point, the subject is not evaluable (NE) at that time point. If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would most likely happen in the case of PD http://recist.eortc.org/recist-1-1-2/.

10.8. Appendix 8: ECOG Performance Status

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

[Oken, 1982]

10.9. Appendix 9: Abbreviations

The following abbreviations and specialist terms are used in this study protocol.

5-FU	5-Fluoruracil
AE	Adverse event
AESI	Adverse event of special interest
ALK	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
ASCO	American Society of Clinical Oncology
ASHI	American Society for Histocompatibility and Immunogenetics
BBB	Bundle branch block
BOR	Best overall response
CAR	Chimeric antigen receptor
CBC	Complete blood count
CDC	Centers for Disease Control
cfDNA	Cell free DNA
CFR	Code of Federal Regulations
CHF	Congestive heart failure
CI	Confidence interval
CMV	Cytomegalovirus
CNS	Central nervous system
CPK	Creatinine phosphokinase
COPD	Chronic obstructive pulmonary disease
CR	Complete response
CRP	C-reactive protein
CRO	Contract Research Organization
CRS	Cytokine release syndrome
CSR	Clinical Study Report
CT	Computerized tomography
CTA	Cancer-testis antigen
CTCAE	Common Terminology Criteria for Adverse Events

DLT	Dose limiting toxicity
DNA	Deoxyribonucleic acid
DoR	Duration of response
DoSD	Duration of stable disease
DRE	Disease related event
EBV	Epstein Barr virus
EC	Ethics Committee
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EDTA	Ethylenediaminetetraacetic acid
EGJ	Esophagogastric junction
EGFR	Epidermal growth factor receptor
EMA	European Medicines Agency
ES	Encephalopathy syndrome
FCBP	Female of childbearing potential
FDA	Food and Drug Administration
FFPE	Formalin-fixed, paraffin embedded
FTIH	First Time In Human
GCP	Good clinical practice
G-CSF	Granulocyte-colony stimulating factor
GFR	Glomerular filtration rate
GGTP	Gamma-glutamyl transpeptidase
GI	Gastrointestinal
GLP	Good laboratory practice
GMP	Good manufacturing practice
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen

HTLV	Human T cell leukemia virus
HPV	Human papilloma virus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council on Harmonization
ICU	Intensive care unit
ID	Identifier
IEC	Independent Ethics Committee
IFN	Interferon
IgG	Immunoglobulin G
IHC	Immunohistochemistry
IL	Interleukin
IMRT	Intensity modulated radiation therapy
IND	Investigational New Drug application
INR	International normalized ratio
ISL	Investigator Safety Letter
IP	Investigational Product
IRB	Institutional Review Board
ITT	Intent-to-Treat
IVD	In vitro diagnostic
mITT	Modified Intent-to-Treat
IV	Intravenous
K-M	Kaplan-Meier
LDH	Lactic acid dehydrogenase
LMO2	LIM domain only 2
LTFU	Long-term follow-up
LTR	Long terminal repeat
LVEF	Left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
MHC	Major histocompatibility complex
mITT	Modified intent to treat
MRCLS	Myxoid/Round Cell Liposarcoma

MRI	Magnetic resonance imaging
MTD	Maximum Tolerated Dose
MUGA	Multiple-gated acquisition scan
NCI	National Cancer Institute
NE	Not evaluable
NIH	National Institutes of Health
NK	Natural killer cell
NS	Normal Saline
NSCLC	Non-small cell lung cancer
NYHA	New York Heart Association
ORR	Overall response rate
OS	Overall survival
OTC	Over the counter
PBMC	Peripheral blood mononuclear cell
PCR	Polymerase chain reaction
PD	Progressive disease
PET	Positron emission tomography
PFS	Progression free survival
PFT	Pulmonary function tests
PI	Principal Investigator
PP	Per protocol
Psi	Packaging Signal
PTT	Partial thromboplastin time
PR	Partial response
qPCR	Quantitative polymerase chain reaction
RCL	Replication competent lentivirus
RCR	Replication competent retrovirus
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic acid
RT	Radiation therapy
SAE	Serious adverse event
SAEW	Serious adverse event worksheet

SAP	Statistical Analysis Plan
SBT	Sequence based typing
SCCHN	Squamous cell carcinoma of the head and neck
SD	Stable disease
SIN	Self-inactivating
SPEAR	Specific Peptide Enhanced Affinity Receptor
SRC	Safety Review Committee
SUSAR	Suspected, unexpected serious adverse reactions
TCR	T cell receptors
TKI	Tyrosine kinase inhibitor
TTR	Time to response
TURBT	Transurethral resection of bladder tumor
ULN	Upper limit of normal
USPI	United States product insert
VEGFR	Vascular endothelial growth factor receptor
VSV-G	Vesicular Stomatitis Virus G glycoprotein
WBC	White blood cell
X-CGD	X-linked chronic granulomatous disease
X-SCID	X linked - Severe combined immunodeficiency disease

10.10. Appendix 10: Protocol Amendment History

None

10.11. References

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