Protocol Number ADP-0022-003

A Phase I Dose Escalation, Open-Label Clinical Trial Evaluating the Safety and Efficacy of MAGE-A10^{c796}T in Subjects with Stage IIIb or Stage IV Non-Small Cell Lung Cancer (NSCLC)

INVESTIGATOR PROTOCOL AGREEMENT PAGE

Protocol Title: A Phase I, Dose Escalation, Open-Label Clinical Trial Evaluating the Safety and Efficacy of MAGE-A10^{c796}T in Subjects with Stage IIIb or Stage IV Non-Small Cell Lung Cancer (NSCLC)

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 on Harmonization (ICH) guideline E6 (r2): Guideline for Clinical Practice (GCP) and all the ethical and regulatory considerations stated. I have read and understood the contents of the MAGE-A10^{c796}T Investigator Brochure

[redacted]	[redacted]
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Date	

CLINICAL STUDY PROTOCOL

Title: A Phase I Dose Escalation, Open-Label, Clinical Trial Evaluating the Safety and Efficacy of MAGE-A10^{c796}T in Subjects with Stage IIIb or Stage IV Non-Small Cell Lung Cancer (NSCLC)

Product Name: MAGE-A10 ^{c796}T

Protocol Number: ADP-0022-003

IND Number: 16508

EudraCT Number: 2016-002518-28

Date of Original Protocol: 06-July-2015

Amendment Number	Date	Reason for Change and Key Revisions
01 (Global)	08-August-2016	This amendment was performed to address questions and comments from Institutional Review Boards and Regulatory Authorities. Additionally, revisions were made based on emerging data from Adaptimmune's clinical program and due to Adaptimmune's newly developed protocol template. Key revisions included the following: Changed phase of trial from Phase I/II to Phase I Revised Background and Study Rationale sections to minimize information already provided in the MAGE-A10^{c796}T Investigator Brochure Revised primary, secondary, and exploratory endpoints to better characterize the safety and efficacy evaluations, and correlative studies to be performed in this study Changed lymphodepleting chemotherapy regimen from cyclophosphamide alone to cyclophosphamide and fludarabine based on emerging data from our ongoing clinical program Added Cell Dose Group 1a, a 3 -6 subject cohort that will receive cyclophosphamide alone to allow for evaluation of this lymphodepleting chemotherapy regimen Decreased expansion phase from 20 to 10 subjects and subsequently removed text regarding the statistical and clinical guidance for expansion

Amendment Number	Date	Reason for Change and Key Revisions
		Removed HLA and antigen expression screening since these tests will be performed in Adaptimmune's Screening Protocol (ADP-0000-001) Revised inclusion/exclusion criteria to provide more clarity on subject population Added guidance on second T cell infusion, including Schedule of Procedures table Added text around the administration of cyclophosphamide and fludarabine, including dose adjustments, prophylactic and supportive treatments Removed irRC criteria for tumor response assessments Added several sections on supportive care guidance, including infection, hematologic and blood product support, autoimmunity, GVHD, and pancytopenia
02 (UK Only)	14-February-2017	Updated Sponsor address. Revised wording of Inclusion criterion #13 for consistency. Updated eligibility criteria for second infusion. The following changes have not been included in the subsequent global amendment and will be maintained in the UK specific amendment: Addition of ECG recordings on Days 2, 3, 5, 6 and 7. Added that sites must have a process in place to inform appropriate intensive care unit (ITU) staff about the study. Added the ADP-0000-001 Screening Study as an Addendum
03 (UK Only)	23-March-2017	Updated to address MHRA requirements that: • UK subjects must be hospitalized for a minimum of 14 days (for safety review) following dosing of the IMP • To clarify that an ITU bed will be made available for emergency use if required

Amendment Number	Date	Reason for Change and Key Revisions
		Additional eligibility criterion to exclude all subjects with a history of brain metastasis in the UK. These changes have not been included in the subsequent global amendment, and will be maintained in the UK specific amendment.
04 (France only)	22-June-2017	The protocol was updated to address the French Ethics committee questions: Added text to state that patients should be hospitalized for 24 hours post infusion. ECG added on Day 2 post infusion. Additional change: Updated Sponsor Study Physician and Sponsor address
05 (Global)	25-August-2017	This amendment was performed to address questions and comments from Regulatory Authorities, Ethics Committees and Investigators. Additionally, revisions were made based on emerging data from Adaptimmune's clinical program and due to Adaptimmune's newly developed protocol template. Appendix 7 contains a summary of and rationale for all revisions for this amendment. Key revisions include the following: Updated Sponsor Study Physician and Sponsor address Clarified text regarding treatment staggers. 21 day stagger will apply to the first 3 subjects to be dosed. Background and rationale for study updated based on changing treatment landscape for NSCLC. Clarified number of subjects treated (rather than enrolled), and added the option for an additional 3 subjects to be treated per cohort upon the Safety Review Committees recommendation. Extended predicted study duration based on enrolment projections. Revised inclusion/exclusion criteria. Added ECG on Day 2.

Amendment Number	Date	Reason for Change and Key Revisions
		Added brain MRI at Screening for subjects with known or suspected CNS metastases, plus brain MRIs at subsequent tumor assessment visits. Deleted CT/MRI at screening, added CT/MRI at Week 4 and moved Week 16 scans to Week 12. Clarifications added around RCL testing and follow up. Refined definition for ITT population Removed reference to legally authorized representative in relation to Informed Consent.
06 (UK only)	20-November-2017	This amendment was performed to incorporate all ADP-0022-003 global amendment 05 changes into an updated UK-specific amendment, which had not already been made and/or were not in conflict with the UK-specific requirements in Amendment 02 and 03. This version also incorporates Amendment 02 dated 30 Oct 2017 to the Screening Protocol ADP-0000-001, which is an addendum to this protocol (Section 17). The primary reason for this protocol amendment was remove all references to NY-ESO-1, however, additional updates have been included. The following changes have been included: updated Sponsor Signatory, Responsible Study Physician; removal of information and references to NY-ESO-1 and LAGE-1a; addition of information and references to MAGE-A4 T; addition of referral sites; update of tumor types under study; clarification of central laboratory for HLA subtyping; incorporation of changes from Protocol Clarification Letters; and updated list of abbreviations.
07 (Global)	31-January-2018	This amendment was created based on emerging data from Adaptimmune's clinical program (see Appendix 7 for full rationale). Group 1b removed as tolerability of this lymphodepletion regimen of cyclophosphamide and fludarabine with the same transduced cell dose of MAGE-A10^{c796}T has been demonstrated in another study (NCT02989064). Subject numbers updated accordingly. Group 2 cell dose range updated to 0.5 to 1.2 x 10^9 transduced cells.

Amendment Number	Date	Reason for Change and Key Revisions
		Lymphodepleting regimen for Group 3 updated based on emerging understanding of lymphodepleting regimens in T-cell therapy. In Group 3, 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 x 10^9 transduced cells in the expansion phase (up to 10 patients in total). 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 will be requested. Amended text regarding treatment staggers. Following a DLT, the 14 day stagger will apply to the next 3 subjects to be dosed. Amended inclusion criteria number 10: Subject has an anticipated life expectancy > 6 months prior to apheresis and >3 months prior to lymphodepletion. Deleted exclusion criteria number 8: Subject has unintended weight loss >10% in 6 months preceding study entry. Eligibility criteria text around HLA amended as HLA results occasionally contain new or rare HLA alleles that should be reviewed in to determine if they are consistent with HLA alleles in the inclusion or exclusion criteria. Exploratory objectives and associated tests updated for accuracy to reflect current available assays and changes in technology. Added text so if a subject completes the interventional phase within three months after receiving T-cells, the following will be performed through Week 12: Concomitant medications, Adverse Events, Hematology, Chemistry, CMV PCR and RCL. Manufacturing timeline updated to approximately 1 month and text added regarding use of unused or leftover patient apheresis material for additional research. Updated SAE reporting process.

Amendment Number	Date	Reason for Change and Key Revisions
		DLT criteria wording amended according to clinical relevance following discussion with Safety Review Committee.
08 (UK only)	26-February-2018	This amendment was performed to incorporate all ADP-0022-003 global amendment 07 changes above into an updated UK-specific amendment.
09 (Global)	14-August-2018	The following updates have been made in this amendment: Incorporated the Long Term Follow Up phase into the protocol including Schedule of Procedures, and updated definitions regarding end of interventional phase and end of study. Added section on supportive care guidance for encephalopathy syndrome (ES). Added text to state that patients should be hospitalized for 72 hours post infusion. Removed treatment stagger during the expansion phase. Added collection of additional blood sample at screening to investigate parameters that may predict manufacturing success. Deletion of Pharmacogenetics sample and analysis. Added serum sample at week 24 and every 3 months until year two: to assess serum proteins and humoral immune responses. Updated timing for first post treatment biopsy to Week 3 (with a window of + 5 weeks) Week 20 visit removed from schedule of assessments. Brain MRI recommended at Screening and required at Baseline for all subjects. Added telemetry monitoring for subjects with known cardiac or pericardial tumor involvement at baseline. Added instructions for symptomatic deterioration/clinical progression in relation to response. Updated eligibility criteria for second infusion.

Amendment Number	Date	Reason for Change and Key Revisions
		Incorporated Protocol clarification letter from 29 March 2018
10 (UK only)	10-September-2018	This amendment was performed to incorporate all ADP-0022-003 global amendment 09 changes above into an updated UK-specific amendment.
11 (Global)	27-February-2019	Change to the lymphodepleting chemotherapy regimen for the Expansion Group Increased the maximum number of cells to be received in the Expansion Group to 15 x 10^9 Updated eligibility criteria for second infusion. Edited language regarding administration of G-CSF Edited language regarding the T-cell Infusion Edited language regarding the supportive care guidance for Pneumocystis Pneumonia Edited language regarding the timing of on-study tumour biopsy Edited language regarding the timing of first on-study CT/MRI scan (Week 4) Change of contact details of Primary Physician Incorporated Protocol clarification letter dated 4 January 2019
12 (UK only)	08-March-2019	This amendment was performed to incorporate all ADP-0022-003 global amendment 11 changes above into an updated UK-specific amendment.
13 (Global)	14-June-2019	Change lymphodepletion regimen for Expansion Group to that used in Group 3 (cyclophosphamide 600 mg/m^2 x 3 days and fludarabine 30 mg/m^2 x 4 days). Updated baseline lab eligibility criteria: increase criteria for baseline ANC, Platelets and GFR. Added upper age limit cap to ≤75 years old. Update exclusion criteria for uncontrolled intercurrent illness to include additional exclusions around history of cardiovascular disease.

Amendment Number	Date	Reason for Change and Key Revisions
		Updated Schedule of Procedures table to correspond with changes related to the lymphodepletion regimen. Stopping rules was updated for any death 'possibly' related to the MAGE-A10^{c796}T to 'probably' related Clarified biopsy collection windows for Baseline and Week 3 time points.

CONFIDENTIALITY STATEMENT

This document contains information which is the property of Adaptimmune Ltd, United Kingdom, and Adaptimmune LLC, USA, and therefore is provided in confidence for your review. It is understood that this information will not be disclosed to others without written approval from Adaptimmune Ltd. or Adaptimmune LLC.

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]

[redacted]

Date

Responsible Study Physician/SAE Contact Information

Role	Name	Day Phone and email	After hours phone	Fax Number
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Sponsor Details

Adaptimmune LLC
351 Rouse Boulevard
Philadelphia, PA 19112
USA

SYNOPSIS

Title: A Phase I Dose Escalation, Open-Label Clinical Trial Evaluating the Safety and Efficacy of MAGE-A10^{c796}T in Subjects with Stage IIIb or Stage IV Non-Small Cell Lung Cancer (NSCLC)	
Short Title	MAGE-A10^{c796}T for advanced NSCLC
Protocol Number	ADP-0022-003
Phase	I
Methodology	This is a first-time-in-human study conducted as an open-label clinical trial in subjects with advanced (Stage IIIb or IV) or recurrent NSCLC. Subjects with the human leukocyte antigen (HLA) HLA-A*02:01 and/or HLA-A*02:06 alleles, whose tumor expresses the MAGE-A10 tumor antigen, and who meet study entry criteria will be eligible to receive autologous genetically modified T-cells expressing enhanced T-cell receptors specific for MAGE-A10 (MAGE-A10^{c796}T). The trial follows a modified 3+3 cell-dose escalation design with an expansion phase at the target cell dose. The trial is conducted with outpatient procedures; however, subjects may be hospitalized for the lymphodepleting chemotherapy at the discretion of the Investigator. It is recommended that the T cell infusion is an inpatient procedure and that patients are hospitalized for 72 hours following dosing to allow for close monitoring of post-infusion adverse events during the dose escalation phase of the study and may be discharged if medically stable at the discretion of the Investigator. Upon enrollment, subjects will undergo leukapheresis for T cell collection, and their cells will be genetically engineered and expanded *ex vivo*. The manufacturing of T cells will take approximately 1 month. Prior to receiving T-cells, subjects will undergo lymphodepleting chemotherapy with cyclophosphamide and fludarabine (see Section 3.1 for lymphodepleting regimen) followed by the T cell infusion on Day 1. Safety and tolerability as well as anti-tumor activity and biomarker assessments to be conducted at each visit are outlined in the Schedule of Procedures. Tumor response will be assessed according to RECIST v 1.1 by Investigators and scans will be collected and stored at a central imaging laboratory for possible independent review. Tumor biopsies for research studies will be taken at Baseline, Week 3, and upon progression of disease. 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 appropriate antigen target may be eligible for a second infusion. Subjects will be considered to have ended the Interventional Phase of the study when he/she has progression of disease, has died before progressing or is withdrawn. Subjects meeting the criteria for disease progression (or withdrawing) prior to Week 12, will be considered to have ended the Interventional Phase of the study only after they have been followed for safety for at least 3 months (up to and including Week 12). Once progression is established, no further efficacy assessments will be collected, other than overall survival. After the Interventional Phase, subjects will continue in the Long Term Follow-up (LTFU) Phase of the study to continue monitoring for potential gene therapy-related delayed adverse events, in accordance with FDA and EMA requirements. LTFU monitoring starts from the T-cell infusion and continues for up to 15 years post last infusion. During the first year post T-cell infusion subjects will be seen in the clinic at 3, 6 and 12 months. From Years 2-5 subjects will be seen in the clinic every 6 months. After 5 years, subjects will be followed up annually for 10 years (i.e. up to Year 15). 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 time of last T cell infusion or discontinued the study for any reason.
Study Duration	It is anticipated that this trial will take approximately 35 months to enroll. Long-term follow up continues for 15 years after the last infusion. The study will be considered complete once the last subject has been followed for 15 years from time of last T cell infusion or discontinued the study for any reason.
Study Center(s)	This is a multi-center study, including approximately 19 sites in North America and Europe. Additional sites may be added at the discretion of the Sponsor.
Number of subjects	Up to 28 subjects treated.

Objectives	**Endpoints**
Primary: To evaluate the safety and tolerability of autologous genetically modified T cells (MAGE-A10^{c796}T)	Toxicity assessment, including Dose Limiting Toxicities (DLT) and determination of optimally tolerated dose range; Adverse events (AE), including serious adverse events (SAE);

	Laboratory assessments, including chemistry, hematology, coagulation, Cardiac assessments, including electrocardiogram (ECG) and cardiac troponin;
Secondary: To evaluate the efficacy of MAGE-A10^{c796}T	Overall Response Rate (ORR) Best Overall Response Time to response Duration of response Duration of stable disease Progression-free Survival (PFS) Overall Survival (OS)
Secondary: To evaluate potential gene therapy-related delayed adverse events for 15 years post infusion	Presence of any of the following LTFU AEs: • New malignancies • New incidence or exacerbation of a pre-existing neurologic disorder • New incidence or exacerbation of a prior rheumatologic or other autoimmune disorder • New incidence of a hematologic disorder • Opportunistic and/or serious infections • Unanticipated illness and/or hospitalization deemed related to gene modified cell therapy Persistence of MAGE-A10^{c796}T and replication-competent lentivirus (RCL) over time.
Exploratory: To evaluate the persistence, [redacted] of transduced MAGE-A10^{c796}T [redacted] T cells.	Correlate persistence, [redacted] of transduced (MAGE-A10^{c796}T) a [redacted] T cells in [redacted] the peripheral blood, [redacted] and/or tumor with response to treatment, [redacted].

Exploratory: Characterize the tumor and tumor microenvironment pre and post- T cell infusion to understand tumor driven determinants of response and resistance to MAGE-A10^{c796}T therapy	Determination of target antigen expression, genes related to antigen processing/presentation, and cell surface co-stimulatory ligands.
Exploratory: Characterize subject serum [redacted] pre and post T cell infusion to understand factors that can influence response or resistance to MAGE-A10^{c796}T therapy.	Evaluation of serum cytokines (e.g. IL-6), [redacted]
Key Inclusion /Exclusion Criteria	Key eligibility include: • Subject is ≥18 to ≤75 years of age on the day of signing informed consent • Subject has histologically or cytologically confirmed diagnosis of advanced non-small cell lung cancer (stage IIIB or IV) or recurrent disease • Subject has received at least one prior line of therapy. • Subjects with known epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase receptor (ALK) or ROS1 gene rearrangements must have failed (progressive disease or unacceptable toxicity) at least one prior EGFR or ALK or ROS1 tyrosine kinase inhibitor where indicated, respectively. Subject may have received PD-1 or PDL-1 inhibitors and or chemotherapy. There is no limit on lines of prior anti-cancer therapy. • Subject has measurable disease according to RECIST v1.1 criteria prior to lymphodepletion. • Subject is HLA-A*02:01 or HLA-A*02:06 positive. Subjects who are HLA-A*02:05, HLA-B*15:01 and/or HLA-B*46:01 positive are NOT eligible.

	• Subject's tumor (either an archival specimen or a fresh biopsy if archival tissue is unavailable) has been pathologically reviewed by a designated central laboratory confirming MAGE-A10 expression. • Subject has an ECOG Performance Status 0-1 and anticipated life expectancy >6 months prior to apheresis and >3 months prior to lymphodepletion. • Subjects with a history of chronic or recurrent (within the last year prior to enrollment) severe autoimmune or active immune-mediated disease requiring steroids or other immunosuppressive treatments are NOT eligible. • Subject with symptomatic CNS metastases are not eligible. Subjects with prior history of symptomatic CNS metastasis must have received appropriate treatment. Refer to protocol Section 4 for complete subject eligibility criteria for study entry.
Investigational Product, Dose, Route, Regimen	The product in this protocol is MAGE-A10^{c796}T (an autologous genetically modified T-cell product) and is administered by infusion. This trial is a dose escalation trial that will evaluate 3 doses of transduced cells administered after a lymphodepleting chemotherapy regimen using a modified 3+3 dose escalation design. The doses for each cell dose group are as follows. **Group 1a*:** 0.1 x10^9 (range: 0.08 x 10^9 to 0.12 x 10^9) transduced cells. **Group 2:** 1 x10^9 (range: 0.5 x 10^9 to 1.2 x 10^9) transduced cells. **Group 3**:** 5 x10^9 (range: 1.2 x10^9 to 6 x10^9) transduced cells. * Group 1a will receive cyclophosphamide 1800mg/m^2/day on Day -7 and Day -6 ** If Group 3 is expanded to 10 subjects, the maximum dose range will be increased to 15 x 10^9 transduced cells for the subjects in the expansion cohort (i.e. after 3-6 subjects are treated in the dose escalation stage)

	Up to a maximum of 10 subjects may be treated at this target cell dose to evaluate safety and efficacy. There will be a 21-day staggering of treatment in between the first 3 subjects treated in the study. For subsequent subjects in the dose escalation phase of the study, a 7-day stagger between treatments will be followed. **NOTE**: If a DLT occurs in Groups 1a or 2 which requires expansion of the group (n=6), then a 14-day stagger would be implemented in the 3 subsequent subjects treated. A second infusion of MAGE-A10^{c796}T cells may only be given to eligible subjects following clinical benefit ≥ 4 weeks after the first T-cell infusion or response to the initial infusion and whose tumor continues to express the appropriate antigen target.
Comparator therapy	None
Statistical Methodology	Descriptive statistics will be provided for selected demographic, safety, response and correlative assessments as outlined in the statistical analysis plan. Descriptive statistics on continuous data will include the mean, median, standard deviation, and ranges, while categorical data will be summarized using frequency counts and percentages. Graphical summaries of the data may be presented.

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1. BACKGROUND AND STUDY RATIONALE

1.1. Non-Small Cell Lung Cancer

Lung cancer is the most common cancer worldwide and it is the leading cause of all cancer-related deaths, responsible for approximately 1 in 5 cancer deaths. There were estimated to be 1.8 million new cases of lung cancer in 2012 (12.9% of the total) (Ferlay, 2013). In the US, lung cancer is the second most common form of cancer after prostate cancer in men and after breast cancer in women (US Cancer Statistics Working Group, 2015). In Europe, lung cancer is also the second most common cancer in men after prostate and the third most common cancer in women after breast and colorectal (Ferlay, 2013). One reason for the relatively poor prognosis is initial diagnosis with advanced disease (only 15% of lung cancers are diagnosed at a localized stage).

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

For early stage NSCLC, surgery is the treatment of choice; however, subsequent relapse at distant sites has resulted in the use of additional chemotherapy or radiotherapy. The treatment paradigms for NSCLC have changed markedly over the last few years and are evolving rapidly. Alongside new chemotherapy agents and combinations, new treatment modalities such as targeted therapy and immunotherapy have come into use in NSCLC and individual drugs are finding or changing their place in treatment. For subjects with advanced NSCLC that have certain molecular alterations, recommended first-line treatment is with targeted therapy such as erlotinib, afatinib or gefitinib for EGFR mutations or crizotinib for ALK rearrangement. For subjects without actionable mutations, first-line therapy is usually with platinum-based doublet chemotherapy. This generally consists of cisplatin or carboplatin with another cytotoxic agent (pemetrexed, taxanes, gemcitabine, vinorelbine or camptothecins), other agents, such as bevacizumab may be added to the regime. In subjects who experience progressive disease (PD), other appropriate targeted therapy agents, single-agent chemotherapy or checkpoint inhibitors (anti-PD-1 antibodies) nivolumab or pembrolizumab are indicated. In addition, pembrolizumab has also now been approved as a first-line treatment of patients with metastatic NSCLC.

1.2. Background to Adoptive T Cell Therapy

Adoptive T cell therapy (ACT) is a treatment that uses a cancer subject's own T lymphocytes with anti-tumor 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 ACT (Kalos, 2013; Klebanoff, 2016; Maus, 2014; Morgan, 2010; Robbins, 2011; Rosenberg, 2008).

The first observations that immune system engagement can lead to antitumor effects are often attributed to William Coley, who observed regression of sarcoma following severe bacterial infections in the 1890s. Further observations of the spontaneous regression of malignant melanoma lesions initially led to the use of T cells isolated from tumor-infiltrating

lymphocytes (TILs). Cell therapy using tumor-reactive TILs has resulted in approximately 50% objective clinical regression in melanoma subjects (Besser, 2010; Dudley, 2005). This therapy, however, has been limited by the requisite surgery to procure tumor-reactive TIL, by *ex vivo* identification and expansion of these cells (TILs could be generated from only 50% of resected samples) and by the failure to reproducibly isolate similar cells from other cancer types.

Adoptive transfer of bulk T lymphocytes obtained from the periphery and expanded *ex vivo* to generate large numbers of cells prior to reinfusion into subjects is an alternative strategy for ACT (Rapoport, 2005). However, tumor cells are well known to be immunologically selected for low antigen presentation and, furthermore, the majority of tumor antigens are normally expressed self-antigens. Hence, the natural T cell receptors (TCRs) that recognize self-tumor antigens are of low affinity. The high tolerance to tumor antigens with normal and/or developmental expression combined with the potent immunosuppressive microenvironment often present at the tumor site is manifest in most cases by suboptimal activation in terms of antitumor activity such that ‘‘native’’ T cells may not be sufficient to induce tumor cell death in most subjects with advanced malignancy. Higher affinity TCRs allow T cells to respond to lower levels of antigen; this is important for tumor immunotherapy where the tumor microenvironment has adapted itself to reduce expression of antigen and also decrease expression of MHC class I molecules (Baccala, 2005; Barrett, 2009; Marincola, 2000).

Therefore, gene-transfer-based strategies have 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 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.

Rational high-throughput genetic mutagenesis approaches have resulted in the ability to molecularly engineer TCRs with substantially higher affinities for target antigens. Affinity-enhanced TCR-based engineering approaches have certain inherent biological advantages, most notably that essentially all cellular proteins can be targeted because the approach is not limited to the targeting of cell surface epitopes, and the primary T cell activation signal is delivered in a physiological context, which may be relevant for optimal functionality of the infused T cells. Additional details are provided in the current MAGE-A10^{796}T Investigator Brochure.

1.3. Adoptive Immunotherapy with MAGE-A10 Specific T Cells and Supporting Data in NSCLC

Although progress has been made in the treatment of lung cancer, improvements have been modest leading to only 4% – 5% improvements in 5-year survival rates for disease Stages I to III and prolongation of only months for Stage IV (Johnson, 2014). In patients with advanced NSCLC, new agent/ platinum combinations have generated overall response rates of approximately 25% – 35% which have plateaued. In addition, time to PD (4 – 6 months), median survival (8 – 10 months), 1 year survival rate (30% – 40%) and 2 year survival rate (10% – 15%) in fit subjects remain short.

However, NSCLC is now recognized as an immunologically targetable disease (Chow, 2013). Recent research into checkpoint inhibitors (e.g. anti-CTLA-4 and anti-PD-1 monoclonal antibodies) have shown promising results in clinical trials but have also demonstrated significant immune-related toxicities (skin, gastrointestinal, hepatic, endocrine, and pneumonitis).

Rates of MAGE-A10 expression in NSCLC in the literature vary from 4.5% to 25% for adenocarcinoma and 38% to 50% for squamous cell carcinoma (Gure, 2005; Tajima, 2003). The Cancer Genome Atlas Ribonucleic Acid (RNA) sequencing database indicates a frequency of expression of 9% in lung adenocarcinoma and 39% in squamous cell carcinoma (NCI, 2016). In-house analysis of MAGE-A10 expression in lung cancer complimentary Deoxyribonucleic Acid (DNA) arrays indicate approximately 24% expression overall and approximately 40% expression in squamous cell carcinoma.

1.4. Rationale for MAGE-A10^{c796}T for NSCLC

Both the potential role for immunotherapies in NSCLC and the high unmet medical need in subjects with advanced disease provide strong rationale for the study of MAGE-A10 SPEAR® T-cells (Specific Peptide Enhanced Affinity Receptor) in the subject population.

1.4.1. Optimization of Lymphodepleting Chemotherapy Regimen

The most common lymphodepletion regimens used in ACT trials to date have incorporated cyclophosphamide or cyclophosphamide and fludarabine (Dudley, 2002; Dudley, 2005; Johnson, 2009; Robbins, 2011). The use of cyclophosphamide alone can achieve lymphodepletion without long term immunosuppressive side effects. However, recent studies in lymphoma, chronic leukemia and acute leukemia using a chimeric antigen receptor (CAR) showed increased CD4+ and CD8+ CAR-T cell expansion, persistence and disease-free survival when fludarabine was added in to a previously cyclophosphamide-only preparative regimen (Turtle, 2016). The cyclophosphamide was administered at 30 – 60 mg/kg x 1 day and fludarabine at 25 mg/m^2/day x 3 – 5 days. Effective lymphodepletion has also been demonstrated in other CAR-T cell studies using cyclophosphamide dosing, together with fludarabine (Batlevi, 2016).

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 anti-tumor 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 30mg/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 (ie. Cohort 1) may be needed to achieve optimal post infusion peak expansion and durable responses in subjects with sarcoma. 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 is acceptable in both. In both cohorts the most frequent adverse events were cytopenia likely attributable to the lymphodepleting chemotherapy. There were no Grade 5 AEs in either cohort.

In this study, increasing lymphodepleting regimens (outlined in Table 1) have been administered including cyclophosphamide 1800mg/m^2/day alone for 2 days (Group 1a), cyclophosphamide 600 mg/m^2 in combination with fludarabine 30mg/m^2 both administered for 3 days (Group 2), and cyclophosphamide 600mg/m^2 in combination with fludarabine 30mg/m^2 both administered for 3 days (Group 3). The safety and tolerability of these lymphodepleting regimen were demonstrated in this study and in the ongoing study of MAGE-A10^{c796}T in urothelial, melanoma and head and neck tumors (ADP-0022-004, NCT02989064). A fourth lymphodepletion regimen consisting of cyclophosphamide 1800 mg/m^2/day for 2 days in combination with fludarabine 30 mg/m^2/day for 4 days was implemented in the Expansion Phase in Amendment 11 based on data from the NY-ESO-1 study, and one subject was treated. However, due to recent safety reports of prolonged pancytopenia with bone marrow hypoplasia in two subjects receiving this higher dose lymphodepletion regimen, the regimen is being reduced to cyclophosphamide 600mg/m^2 for 4 days in combination with fludarabine 30mg/m^2 or 3 days. The reduction in cyclophosphamide dose may limit the depth and duration of cytopenias. In addition, cyclophosphamide is associated with cardiotoxicity including supraventricular arrhythmias, and a lower dose may therefore further reduce the risk of cardiovascular events. No subjects received this lymphodepletion regimen in this trial. With the implementation of this Amendment (13), the study will revert back to the Group 3 lymphodepletion regimen for the remainder of the Expansion Group.

Refer to Section 3.2.3 for further rationale for lymphodepletion**.**

2. TRIAL OBJECTIVES AND ENDPOINTS

Objectives	**Endpoints**
Primary	
To evaluate the safety and tolerability of autologous genetically modified T cells (MAGE-A10^{c796}T)	Toxicity assessment, including Dose Limiting Toxicities (DLT) and determination of optimally tolerated dose range; Adverse events (AE), including serious adverse events (SAE); Laboratory assessments, including chemistry, hematology, and coagulation Cardiac assessments, including electrocardiogram (ECG) and cardiac troponin);
Secondary	

To evaluate the efficacy of MAGE-A10^{c796}T	Overall Response Rate (ORR) Best Overall Response Time to response Duration of response Duration of stable disease Progression-free Survival (PFS) Overall Survival (OS)
To evaluate potential gene therapy-related delayed adverse events for 15 years post infusion.	Presence of any of the following LTFU AEs: • New malignancies • New incidence or exacerbation of a pre-existing neurologic disorder • New incidence or exacerbation of a prior rheumatologic or other autoimmune disorder • New incidence of a hematologic disorder • Opportunistic and/or serious infections • Unanticipated illness and/or hospitalization deemed related to gene modified cell therapy Persistence of MAGE-A10^{c796}T and replication-competent lentivirus (RCL) over time.
Exploratory	
Exploratory: To evaluate the persistence, [redacted] of transduced MAGE-A10^{c796}T [redacted] T cells.	Correlate persistence, [redacted] of transduced (MAGE- A10c796T) [redacted] T cells in [redacted] the peripheral blood, [redacted] and/or tumor with response to treatment, [redacted].
Exploratory: Characterize the tumor and tumor microenvironment pre and post- T cell infusion to understand tumor driven determinants of response and resistance to MAGE-A10^{c796}T therapy	Determination of target antigen expression, genes related to antigen processing/presentation, and cell surface co-stimulatory ligands.
Exploratory: Characterize subject serum [redacted] pre and post T cell infusion to understand factors that can influence response or resistance to MAGE-A10^{c796}T therapy.	Evaluation of serum cytokines (e.g. IL-6), [redacted]

3. INVESTIGATIONAL PLAN

3.1. Overall Study Design

This is a Phase I, first time in human study of genetically engineered MAGE-A10^{c796} T cells in subjects who are positive for HLA-A*02:01 or HLA-A*02:06 and negative for HLA-A*02:05, HLA-B*15:01 and HLA-B*46:01 and have advanced NSCLC. Up to 28 subjects overall may be treated.

Using a modified 3+3 cell dose-escalation design, the study will treat 16-28 subjects including an expansion cohort of up to 10 subjects at the target cell dose to further characterize safety and any preliminary evidence of antitumor activity. The Safety Review Committee (SRC) may recommend adding additional patients to a given group (not to exceed 9 subjects in total in any group apart from target dose expansion group), see Section 3.3, resulting in a potential maximum number of 28 subjects treated. Additional subjects may be enrolled to compensate for enrolled subjects who did not receive T cell infusion. If a subject has been enrolled to the study and leukapheresis has been performed, then they may be permitted to receive the T-cell infusion even if 10 patients have been treated, provided the benefit-risk assessment is favorable. This would require sponsor approval. As per the original design of the protocol, cyclophosphamide alone as the lymphodepleting chemotherapy will be evaluated in 3 – 6 subjects (Group 1a) prior to introduction of cyclophosphamide and fludarabine as the lymphodepletion regimen. All cell dose numbers will be estimated based on transduced (not total) cells. Three cell doses of MAGE-A10^{c796}T will be assessed as defined in Table 1:

Table 1: Cell Dose Groups

Group	Number of Subjects	Lymphodepleting Chemotherapy	Transduced cells[1]	Interval for Safety Review
1a	3 - 6	Cyclophosphamide 1800mg/m^2/day on Days -7 and -6	0.1 x 10^9 (range: 0.08 x 10^9– 0.12 x 10^9)	21-day stagger between first 3 subjects treated
2	3 - 6	Cyclophosphamide 600mg/m^2/day and fludarabine 30 mg/m^2/day on Days -7, -6 and -5	1 x 10^9 (range: 0.5 x 10^9– 1.2 x 10^9)[3]	7-day stagger[2]
3	3 - 6[4]	Cyclophosphamide 600mg/m^2/day on Days -7, -6, -5 and fludarabine 30 mg/m^2/day on Days -7, -6, -5 and -4	5 x 10^9 (range: 1.2 x 10^9 – 6 x 10^9)	7-day stagger[2]
	Expansion phase: Up to 10 subjects in total in Group 3[5]	Cyclophosphamide 600mg/m^2/day on Days -7, -6, -5 and fludarabine 30 mg/m^2/day on Days -7, -6, -5 and -4	5 x 10^9 (range: 1.2 x 10^9 – 15 x 10^9)[3]	7-day stagger among the first three subjects who receive transduced cells at >6 x 10^9 only; No stagger if transduced cells ≤6 x 10^9

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 will be requested.
2. If in any Group, 1 out of 3 subjects experiences a DLT requiring expansion of an additional 3 subjects (n=6), the observation period will be increased from 7 days to 14 days for the 3 subsequent treated subjects.
3. If Group 3 is expanded to 10 subjects, the maximum dose range will be increased to 15 x 10^9 transduced cells for the subjects in the expansion cohort (i.e. after 3-6 subjects are treated in the dose escalation stage). The Safety Review Committee (SRC) may recommend adding additional patients to a given group (not to exceed 9 subjects in total in any group apart from target dose expansion group). There will be a 7-day stagger among the first three subjects in the Expansion phase who receive transduced cells at >6 x 10^9.
4. On November 30, 2018, the Safety Review Committee (SRC) supported the proposal to open the Expansion Group after 2 rather than 3 subjects were treated in Group 3 dose escalation as a total of 7 subjects (2 in this study and 5 in ADP-0022-004) were treated with this cellular therapy at the same dose level and demonstrated acceptable safety.
5. One subject in the Expansion phase was treated with the lymphodepleting regimen consisting of cyclophosphamide 1800mg/m2/day on Days -3 and -2 and fludarabine 30 mg/m2/day on Days -5, -4, -3 and -2 (Section 1.4.1) per Amendment 12.

Subjects will have pre-screened in Screening Protocol, ADP-0000-001, for the presence of HLA-A*02:01, HLA-A*02:06 and MAGE-A10 expression on the tumor. The absence of HLA*02:05, HLA-B*15:01 and/or HLA-B*46:01 will also have been assessed.

Subjects who have pre-screened for the relevant HLA alleles and MAGE-A10 tumor antigen will sign the study (ADP-0022-003) Informed Consent Form (ICF) and enter the Screening Phase in this protocol to determine eligibility for the study. If the subject meets the study eligibility criteria (Section 4.2), the subject begins the Interventional Phase of the study. A subject will be considered to have ended the Interventional Phase of the study when he/she

has progression of disease or has died before progressing, or is withdrawn (see Section 4.5). Subjects that have Progressive Disease (PD) or withdraw prior to 12 weeks post T-cell infusion will be considered to have ended the Interventional Phase of the study only after they have been followed for safety for 12 weeks post infusion (see Section 4.5)

After the Interventional Phase, subjects will continue in the Long Term Follow-up (LTFU) Phase of the study to continue monitoring for potential gene therapy-related delayed adverse events for 15 years post infusion (Section 7.4.8). A subject will be considered to have ended the study when he/she has been followed for 15 years from time of last T cell infusion or discontinued the study for any reason.

Leukapheresis is performed to obtain cells for the manufacture of autologous MAGE-A10^{c796} TCR bearing T cells. Leukapheresis should be performed as soon as possible after the subject is determined to be eligible for study participation. Leukapheresis may also be performed in advance of a subject being eligible for treatment (i.e., before meeting the eligibility criteria prior to lymphodepleting chemotherapy).

When the MAGE-A10^{c796}T cells are available, subjects will undergo lymphodepleting chemotherapy with cyclophosphamide alone (Group 1a) or cyclophosphamide and fludarabine (Section 5.2), followed by infusion of MAGE-A10^{c796}T cells (Section 5.3 and Table 1). Prior to the administration of lymphodepleting chemotherapy, subjects must have received at least one prior line of treatment and have measurable disease. Eligibility criteria for lymphodepletion will be confirmed and baseline tumor assessment obtained. The lymphodepleting chemotherapy may be given as an outpatient procedure but subjects may be hospitalized at the discretion of the Investigator. Subjects should receive granulocyte-colony stimulating factor (G-CSF) support starting on Day -3. It is recommended that the T cell infusion is an inpatient procedure and that patients are hospitalized for 72 hours post infusion to allow for close monitoring of post-infusion AEs during the dose escalation phase of the study and may be discharged if medically stable at the discretion of the Investigator. Subject may be hospitalized for follow-up care post T-cell infusion at the discretion of the Investigator. Section 8 provides guidance for supportive care during T-cell infusion.

The time point for administration of lymphodepleting chemotherapy and subsequent infusion of MAGE-A10^{c796}T cells will be staggered for subjects within groups and between groups to permit ongoing data review as described herein:

- The first 3 subjects to be treated in the study may receive lymphodepleting chemotherapy as defined in Table 1 only after the previously treated subject has had a minimum safety observation period of 21 days following their MAGE-A10^{c796}T cell infusion.
- Subsequent subjects in any dose escalation Group may receive lymphodepleting chemotherapy as defined in Table 1 only after the previously treated subject has had a minimum safety observation period of 7 days following their MAGE-A10^{c796}T infusion. In effect, this would result in a minimum observation period of 14 days from MAGE-A10^{c796}T cell infusion in the preceding subject before a new subject could be infused.

NOTE: If in Groups 1a or 2, 1 out of 3 subjects experiences a DLT requiring expansion of an additional 3 subjects (n=6), the observation period in the subsequent 3 subjects will be increased from 7 days to 14 days.

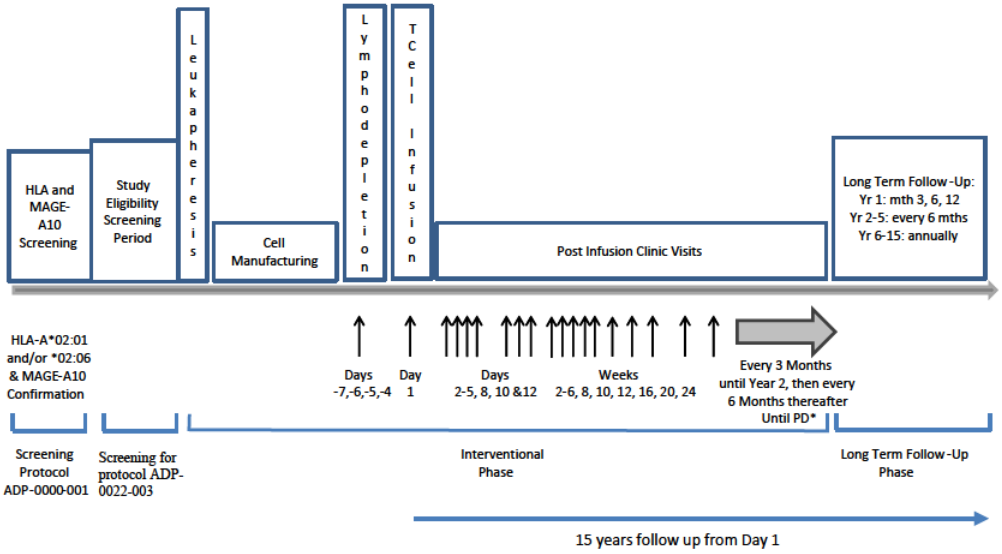
Safety will be reviewed on an on-going basis on all treated subjects before a new subject is infused with T cells and regular safety review meetings will be held (refer to Section 3.3).

Efficacy, safety, and biomarker assessments to be conducted at each visit are outlined in the Schedule of Procedures (Table 6). Efficacy will be assessed using RECIST v1.1 (Eisenhauer, 2009).

Subjects who have clinical benefit ≥ 4 weeks after the first T-cell infusion or response to the initial infusion but whose tumors continue to express the MAGE-A10 antigen will be eligible for a second infusion with engineered T-cells, pending they meet eligibility criteria defined in Section 4.4. Refer to Table 17 for Schedule of Procedures for Second Infusion (Interventional Phase – Infusion 2).

After the Interventional Phase of the study, subjects will continue in the long term follow-up (LTFU) Phase of the study to continue monitoring of gene therapy-related delayed AEs for 15 years post-infusion in accordance Food and Drug Administration (FDA) and European Medicines Agency (EMA) follow up requirements for gene therapy clinical trials. During the first year post T cell infusion subjects will be seen in the clinic at 3, 6 and 12 months. From Year 2-5 subjects will be seen in the clinic every 6 months. After 5 years, the subjects will be followed up annually for up to 10 years (i.e. up to Year 15). All subjects will continue to be followed for OS during the LTFU phase.

Figure 1 provides a schematic for the study.



*subjects who have a confirmed response (or have clinical benefit ≥ 4 weeks after the first T-cell infusion) and whose tumors continue to express MAGE-A10 as verified by assay performed in biopsied tissue, can be considered for a second infusion with engineered T-cells

Figure 1: Schematic for Study ADP-0022-003

3.2. Rationale for Components of Study Design

3.2.1. Screening for HLA and MAGE-A10 (ADP-0000-001)

The MAGE-A10^{c796}T specifically recognizes the HLA-A*02:01 and HLA-A*02:06-restricted MAGE-A10 peptide antigen GLYDGMHLY; therefore, this protocol will enroll subjects with these two most common HLA-A2 allelic variants. Furthermore, the TCR MAGE-A10^{c796}T can interact with specific HLA molecules independently of the peptide presented, which could lead to graft versus host disease (GVHD). Therefore, there are 3 exclusion HLA class I alleles: HLA-A*02:05, HLA-B*15:01 and HLA-B*46:01 and the subject must not possess ANY of these alleles.

The prevalence of HLA sub-types varies from population to population. Information on the prevalence of HLA-A2 allelic variants is available in the Allele Frequency Net Database (www.allelefrequencies.net). It is recommended that Investigators review the database for HLA-A2 allelic variants relevant to the study population at their site.

3.2.2. T Cell Manufacturing

The Investigational Product is comprised of autologous CD4 and CD8 T cells that have been transduced with a self-inactivating (SIN) lentiviral vector expressing an affinity enhanced MAGE-A10 specific TCR. The product of this transduction is polyclonal T cells which are designed to target MAGE-A10 in tissue. The transfer vector is a SIN lentiviral vector which has been meticulously designed to contain only the minimal genetic elements required for function, and no vector proteins for maximum biosafety (Dull, 1998). Lentiviral vectors are a subset of retroviral vectors thought to have an enhanced safety profile. 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 in comparison to the γ retroviral vectors (Maruggi, 2009; Modlich, 2009; Montini, 2009; Montini, 2006).

For subjects whose cells fail to meet the cell dose requirement during the manufacturing process, re-leukapheresis and/or re-manufacturing will be requested.

Cell product is typically ready to be shipped to the site approximately 1 month after leukapheresis. Shipment to clinical sites will ideally be before the start of lymphodepleting chemotherapy. Any unused or leftover patient apheresis may be used by the sponsor for performing additional research studies to modify or improve the manufacturing process.

Additional manufacturing details are provided in the MAGE-A10^{c796} T Investigator Brochure.

3.2.3. Lymphodepletion

The incorporation of lymphodepletion prior to ACT 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 lymphocyte (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.

Recent evidence suggests that preparation for successful engraftment and expansion of gene modified ACT 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 ACT including a chimeric antigen receptor showed increased T cell expansion, persistence and disease-free survival when fludarabine was added in a previously cyclophosphamide-only preparative regimen (Turtle, 2016).

Based on the experience using combination fludarabine-cyclophosphamide lymphodepleting chemotherapy in the NY-ESO-1 study in subjects with synovial sarcoma (NCT01343043, see Section 1.4.1) and the increasing evidence that fludarabine is a key component of the adoptive T cell therapy, the lymphodepleting regimens in this study have been outlined in Table 1. Additionally, given the safety and efficacy of cyclophosphamide administered in combination with fludarabine (Section 1.4.1), future patients treated in the Expansion Group will be treated with a lymphodepletion regimen consisting of cyclophosphamide 600 mg/m2/day for 3 days in combination with fludarabine 30 mg/m^2/day for 4 days.

3.2.4. T Cell Infusion

The investigational product in this study is the infusion of autologous T cells transduced with lentivirus encoding enhanced TCR specific for MAGE-A10 (refer to 5.3 for administration details).

3.2.5. Rationale for MAGE-A10^{c796}T Cell Dose

In determining the starting cell dose, rate of dose escalation and target cell dose in this study, consideration was given to the safety and activity profile of MAGE-A10^{c796}T in preclinical studies, the affinity of the TCR, the clinical safety profile of similar products and the number of transduced cells.

The pre-clinical safety and activity profile of MAGE-A10^{c796}T appears similar to that of NY-ESO-1^{c259}T. In preclinical testing, no off-target recognition by the MAGE-A10 TCR has been identified. Furthermore, the MAGE-A10 antigen expression is tumor specific, with no detectable expression in normal adult tissues other than testis and placenta. Therefore, the safety profile of the target and the TCR are excellent and support a less conservative dose escalation strategy.

As of February 2019, this study and the ongoing study of MAGE-A10^{c796}T in urothelial, melanoma and head and neck tumors (ADP-0022-004, NCT02989064) have treated 5 (two in the present study and three in the multi-tumor study) of a total of 18 subjects with 5-6 x 10^9 transduced cells without untoward AEs related to the cellular product. In addition, in the ongoing MAGE-A4 A4^{c1032}T (ADP-0022-001, NCT03132922) in subjects with multiple malignancies, 11 subjects have been treated with over 5 x 10^9 transduced cells with 5 subjects receiving 9-10 x 10^9 transduced cells. While there was one DLT (Grade 4 CRS) in the in the first subject treated on the MAGE-A10 ^{c796}T NSCLC study who received 0.1 x 10^9 (+/- 20%) transduced cells, there were no other DLTs in the remaining 17 subjects of which 9 received more than 1 x 10^9 transduced MAGE-A10 ^{c796}T. In addition, there were no DLTs in the MAGE-A4 A4^{c1032}T (ADP-0022-001) study. In summary, there has been no clear association between the frequency or severity of AEs and transduced cell dose in the subjects treated to date and there has been no evidence of off-target toxicity or alloreactivity.

Current experience with another TCR product, NY-ESO-1^{c259}T is with cell doses in the range of ~<1 – 15 x 10^9 transduced cells in subjects with synovial sarcoma. Five out of 12 subjects in Cohort 1 received > 5 x 10^9 transduced cells, with one subject receiving 14 x 10^9 transduced cells. AEs were reported in all subjects, with no differences noted in subjects who received higher transduced cell doses (>5 x 10^9 cells, D'Angelo 2018). In addition, 38 subjects with synovial sarcoma (n=18) and melanoma (n=20) in the study "Chemotherapy Followed by ESO-1 Lymphocytes and Aldesleukin to Treat Metastatic Cancer (NCT00670748)" received total T cell doses from 9-130 x 10^9 with transduced cell doses from 9-109 x 10^9 (mean 38 x 10^9) without reported toxicity due to the Tcell infusion. Furthermore, there was a suggestion of a relationship between clinical response with a minimum T cell dose exceeding 10x10^9 transduced cells (Robbins, 2015).

Given that this study and a similar study using the same TCR treated a total of 18 subjects without a clinical response, this amendment proposes to maximize the lymphodepletion regimen (see Section 1.4.1 and 3.2.2) and increase the number of transduced cells in the Expansion Phase. As shown in Table 1, 1.2 to 15 x 10^9 MAGE-A10^{c796}T transduced cells may be administered to subjects. Given that 5 subjects in this study together with study ADP-0022-004 have received 5-6 x 10^9 MAGE-A10^{c796}T transduced cells with an acceptable safety profile and without evidence of off-target toxicity or alloreactivity, a 7-day stagger will be introduced only among the first 3 subjects treated at >6 x 10^9 MAGE-A10^{c796}T transduced cells. Subjects treated with ≤6 x 10^9 MAGE-A10^{c796}T transduced cells will be entered on study without a stagger. MAGE-A10^{c796}T transduced cells will be administered by a single

intravenous (IV) infusion. Patient safety for these MAGE-A10^{c796}T studies will continue to be evaluated by the SRC (see Section 10.3) and routine pharmacovigilance measures.

In summary, there is considered to be favorable benefit:risk for higher cell doses (up to 15 x 10^9 transduced cells) with MAGE-A10^{c796}T based on: 1) the absence of off-target toxicity or alloreactivity, the absence of clinical response and the acceptable safety profile to date, and 2) the possible relationship between a transduced cell dose threshold and clinical response with the reported safety of infusion of higher cell doses in the above referenced publication.

3.3. 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 4.0.

A DLT is defined as

- Any clinical toxicity of Grade 3 or higher (using NCI CTCAE v4.0) regardless of 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 infusion of MAGE-A10^{c796}T 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, a Safety Review Committee (SRC) will assess whether the toxicity is deemed a DLT (refer to Section 10.3 for details of the SRC). Two DLTs in one group will not automatically result in determination of a MTD. For these events, the Safety Review Committee (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 10.3 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 Regulatory Authorities according to the standards for expedited reporting defined in Section 9.6.

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 or 4 CRS or toxicities related to CRS resolving to Grade ≤ 2 within 7 days;
- Grade 3 graft versus host disease (GVHD) or toxicities related to GVHD;
- 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 or fatigue not resolved to Grade ≤2 within 7 days

If there are no DLTs in any of the first 3 subjects treated in Groups 1a, and 2, then lymphodepletion and treatment can proceed into the next higher dose. If one subject develops a DLT at a specific cell dose, then an additional three subjects will be treated in that same dose group. Note: the Safety Review Committee (SRC) supported the proposal to consider Group 1a complete and to dose escalate to treatment Group 2 after 5 rather than 6 subjects treated (on 28Mar2018), see Appendix 7 for full rationale.

Development of DLTs in more than 1 out of 6 subjects in a specific dose group may suggest that the maximum tolerated dose (MTD) has been exceeded. However, a clear relationship between cell dose and toxicity has not been established in the context of T-cell gene therapy. Moreover, a 3+3 design is associated with high variability of MTD estimates. Therefore, the emergence of a DLT in more than 1 out of 6 subjects within a given group will trigger a temporary pause in enrollment to allow for an overall assessment of the safety data observed to date by the SRC. The SRC may recommend adding additional patients to a given group. The sample size of the target cell dose may be expanded up to 10 subjects (inclusive of the subjects treated in the cell dose escalation phase) to characterize safety and any preliminary evidence of antitumor activity. The cell dose in the Expansion group will be the highest cell dose studied even if no DLTs are observed.

Throughout the conduct of the study, safety data will be reviewed for each subject on an ongoing basis. Additionally, periodic safety reviews will be undertaken by a SRC. Following such review, a decision whether to halt the study; modify the dose and/or study [i.e. treat additional subjects (not to exceed 9 subjects in total in any group apart from target dose expansion group) to further characterize safety]; or continue enrollment will be made. Decisions will be based on the nature of the DLTs observed as defined above. Adaptimmune's Safety Governance Board will have final decision-making authority, in collaboration with the SRC and Investigators.

3.4. Number of Subjects and Duration of Study

The target number of subjects treated in this trial is 16-28 subjects including up to 10 subjects at the target dose to better characterize the efficacy and safety of the T cells. The Safety Review Committee (SRC) may recommend adding additional patients to a given group (not to exceed 9 subjects in total in any group apart from target dose expansion group), see Section 3.3, resulting in a potential maximum number of 28 subjects treated.

If a subject has been enrolled to the study and leukapheresis has been performed, then they may be permitted to receive the T-cell infusion even if 10 patients have been treated at the

target dose, provided the benefit-risk assessment is thought to be favorable. This would require sponsor approval.

Study enrollment is expected to continue for approximately 35 months. The Interventional Phase of the study will be considered to have ended once the last treated subject has transitioned to the Long Term-Follow up Phase. Long-term follow up continues for 15 years after the last infusion. This trial will remain open until all enrolled subjects have been followed for 15 years post T cell infusion (per FDA and EMA Guidance) or discontinued the study for any reason. The study will be considered complete once the last subject has been followed for 15 years from the time of last T cell infusion or discontinued from the study for any reason.

3.5. Sites

The protocol will be conducted in approximately 19 sites in North America and Europe. The number of centers is necessary to ensure recruitment in this targeted population. Additional centers may be added at the discretion of the Sponsor.

3.6. Benefit: Risk Assessment

The results of non-clinical and planned clinical studies conducted with MAGE-A10^{c796}T are summarized in the Investigator's Brochure. This section outlines the potential benefits, risks and the mitigation strategy for this study.

3.6.1. Benefit Assessment

The MAGE-A10 cancer/testis antigen is expressed by immunohistochemistry (IHC) in approximately 9% of lung adenocarcinoma, 26% of squamous cell carcinoma, and 19% of large cell carcinoma and is highly restricted to the tumor and not expressed in normal healthy adult tissues. A subject'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 CAR-T cells) 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.

The efficacy of MAGE-A10^{c796}T has not been evaluated as of yet. Efficacy however, has been demonstrated with other adoptive T-cell therapies (ACT), including NY-ESO-1^{c259}T. This supports the potential therapeutic benefit of TCR therapy in patients with malignancies expressing the relevant antigen.

As of 27 January 2017, 64 subjects have been treated with NY-ESO-1^{c259}T (engineered using a lentiviral vector) in five clinical trials in the indications of multiple myeloma, synovial sarcoma, melanoma, and ovarian cancer. Additionally, 38 subjects were treated in an Investigator sponsored study conducted by the NCI, where the T cells were modified using a retroviral vector, expanded using NCI cell processing methods and administered in conjunction with IL-2 (Robbins, 2008; Zhao, 2007). Two subjects with gastroesophageal cancer have been treated in the ATTACK-OG clinical trial. Objective responses have been observed in subjects with sarcoma, myeloma and melanoma (Robbins, 2015; Rapoport, 2015;

D'Angelo 2019). In subjects with advanced myeloma, NY-ESO-1^{c259}T has been investigated in the context of melphalan and autologous hematopoietic stem cell transplant (auto-HSCT). Fifty nine percent (59%) of subjects had a best response of near complete response (CR) or CR and 32% had partial responses (PR) (Rapoport, 2015). The duration of response exceeded 1 year in 10 subjects; 8 of these lasting more than 2 years. Gene modified T cells persisted in all but one patient who had reached at least 2 years post T cell administration. In subjects with unresectable synovial sarcoma, 12 subjects were treated with NY-ESO-1^{c259}T and six responded (1 CR and 5 PRs). Median duration of response was more than 6 months (D'Angelo, 2019). Efficacy was also shown with NY-ESO-1^{c259}T in Investigator sponsored studies with synovial sarcoma and melanoma.

3.6.2. Risk Assessment

The study incorporates several measures to address the risks including: (1) extensive preclinical evaluation of the MAGE-A10^{c796}T which has incorporated learnings from other ACT programs (MAGE-A10^{c796}T Investigator Brochure); (2) based on the preclinical alloreactivity data, exclusion of subjects with HLA-A*02:05, HLA-B*15:01 and/or HLA-B*46:01; (3) a validated clinical trial assay with precision and reproducibility for the selection of patients with MAGE-A10 expression in their tumors; (4) step-wise escalation of the T cell dose and lymphodepletion regimen; (5) staggered treatment in the cell dose escalation groups, such that there is a 21-day/7-day observation period after T cell infusion between treatment of subjects; (6) treatment in a specialized academic center experienced with management of toxicities associated with autologous T cell therapies; and (7) a Safety Review Committee including expertise external to Adaptimmune to evaluate safety throughout the study.

It is anticipated that certain toxicities observed with NY-ESO-1^{c259}T are common to other ACTs and would be expected to occur with MAGE-A10c^{796}T. Most of these toxicities are also observed with standard of care chemotherapies or with checkpoint inhibitors. Cytokine release syndrome, autologous GVHD and encephalopathy syndrome (ES) are toxicities observed with ACTs and not typically observed with the current standard of care therapies. Pancytopenia has been observed after initial bone marrow recovery from high-dose chemotherapy followed by infusion of NY-ESO-1^{c259}T-cells. Therefore, guidelines for management of these toxicities are included in the protocol (Section 8). Furthermore, to manage the risk of these toxicities in the MAGE-A10^{c796}T program, Adaptimmune is implementing specific AE pages in the electronic case report form (eCRF) to carefully document these events to enable evaluation and identification of potential risk factors. The ACTs are generally administered once. An advantage of this modality of therapy is that the vast majority of toxicities resolve within 4 – 6 weeks after T cell infusion.

3.6.3. Overall Benefit: Risk Conclusion

Subjects with advanced or metastatic NSCLC who have progressed following other therapies, constitute a population with a high unmet medical need. Preclinical studies support the specificity, safety, and anti-tumor activity of MAGE-A10^{c796}T cells. The clinical study has taken measures to ensure safe administration of the MAGE-A10^{c796}T with close monitoring for toxicities, and guidelines for management of these toxicities based on prior experience with other TCRs. Therefore, the benefit: risk balance supports initial testing of MAGE-A10^{c796}T in the clinic in the defined study population.

4. SELECTION OF STUDY POPULATION, WITHDRAWAL, COMPLETION AND STOPPING CRITERIA

4.1. Overview

Subjects will be assessed for eligibility for study participation prior to leukapheresis AND prior to lymphodepleting chemotherapy.

NOTE: Refer to Section 4.2.2 and Section 4.3 to understand the time restrictions (i.e., wash-out period) required for therapies (anti-cancer treatments, radiotherapy, and corticosteroids) prior to leukapheresis and lymphodepleting chemotherapy, respectively, to ensure subject eligibility and proper timing of procedures.

Prior to leukapheresis and for qualification for the study, all subjects must meet all inclusion and exclusion criteria defined in Section 4.2.

4.2. Eligibility Criteria for Study Participation (Prior to Leukapheresis)

4.2.1. Inclusion criteria

1. Subject 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. Subject is ≥18 to ≤75 years of age on the day of signing informed consent.
4. Subject has a diagnosis of histologically or cytologically confirmed advanced non-small cell lung cancer (Stage IIIB or IV) or recurrent disease.
5. Subjects with known EGFR mutations or ALK or ROS1 gene rearrangements have failed (PD or unacceptable toxicity) at least one prior EGFR or ALK or ROS1 tyrosine kinase inhibitor (TKI) where indicated, respectively. There is no limit on lines of prior anti-cancer therapy.
6. Subject has received or is receiving at least one line of prior therapy
7. Subject is HLA-A*02:01 and/or HLA-A*02:06 positive. The sponsor/sponsor's representative will review the results of HLA typing for inclusion and exclusion alleles and will adjudicate patient eligibility based on HLA results
8. Subject's tumor (either an archival specimen or a fresh biopsy if archival tissue is unavailable) has been pathologically reviewed by an Adaptimmune designated central laboratory confirming MAGE-A10 expression.
9. Subject has Eastern Cooperative Oncology Group (ECOG) Performance Status 0-1 (Oken, 1982).
10. Subject has an anticipated life expectancy > 6 months prior to apheresis.
11. Subject has left ventricular ejection fraction ≥50%.

12. Subject is fit for leukapheresis and adequate venous access can be provided for the cell collection.
13. Female patients of childbearing potential (FPCP) must have a negative urine or serum pregnancy test. **NOTE**: FPCP is defined as premenopausal and not surgically sterilized. FPCP must agree to use effective birth control or to abstain from heterosexual activity throughout the study, starting at the first dose of lymphodepleting chemotherapy through 12 months after the infusion of cells or for 4 months after there is no evidence of persistence/gene modified cells in the blood, whichever is longer. Effective contraceptive methods include intra-uterine device, oral or injectable hormonal contraception, or 2 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.

    OR

    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).

    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 ERCs/IRBs. Periodic abstinence (e.g., calendar, ovulation, sympto-thermal, post-ovulation methods, etc.) and withdrawal are not acceptable methods of contraception.
14. Subject must have adequate organ function as indicated by the following laboratory values in Table 2.

Table 2: Laboratory Values to Define Adequate Organ Function

System	Laboratory Value
Hematological	
Absolute Neutrophil count (ANC)	≥1.5 x 10^9/L (without G-CSF support)
Platelets	≥100 x 10^9/L (without transfusion support within 7 days prior to leukapheresis and lymphodepletion)
Hemoglobin	>80 g/L (without transfusion support within 7 days from start of leukapheresis and lymphodepletion)
Coagulation	
Prothrombin Time or International Normalized Ratio	≤1.5 x upper limit of normal (ULN) unless receiving therapeutic anticoagulation.
Partial Thromboplastin Time	≤1.5 x ULN unless receiving therapeutic anticoagulation.
Renal	
Calculated or measured creatinine clearance[1]	≥ 60 mL/min
Hepatic	
Serum total bilirubin	≤1.5 x ULN (unless subject had documented Gilbert's Syndrome)
ALT/Serum Glutamic Pyruvic Transaminase	≤2.5 x ULN
1. Creatinine clearance will be calculated using the Cockcroft-Gault Method: $\text{Creatinine clearance} = \frac{(140 - \text{age}) \times \text{weight kg}}{72 \times \text{serum creatinine mg/dL}} (\times 0.85 \text{ in females})$ Or by 24-hour urine creatinine collection or by nuclear medicine ethylenediamineteraacetic acid (EDTA) glomerular filtration rate (GFR) measurement, or diethylene triamine pentaacetic acid (DTPA) according to standard practice at the treating Institution.	

4.2.2. Exclusion criteria

A subject meeting any of the following criteria is not eligible for participation in the study:

1. Subject has received:
   - Cytotoxic chemotherapy within 3 weeks prior to leukapheresis;
   - Immune therapy (including monoclonal antibody therapy, checkpoint inhibitors) or biological therapy within 2 weeks prior to leukapheresis;
   - Corticosteroids or any other immunosuppressive therapy within 2 weeks prior to leukapheresis;

NOTE: recent or current use of inhaled or topical steroids is not exclusionary. Other exceptions are also provided for specific systemic steroid use in Section 6.1.

- Small molecules/Tyrosine kinase inhibitors and any other anti-cancer treatment associated with myelosuppression within 1 week prior to leukapheresis. Note: no washout period is required for selective EGFR and ALK/ROS-1 inhibitors, unless they are multi-kinase inhibitors targeting VEGFR, PDGFR, or c-Kit receptors.
- Investigational treatment within 4 weeks prior to leukapheresis;
- Any prior gene therapy using an integrating vector.

2. Subject is HLA-A*02:05, HLA-B*15:01 and/or HLA-B*46:01 positive. The sponsor/sponsor's representative will review the results of HLA typing for inclusion and exclusion alleles and will adjudicate patient eligibility based on HLA results.
3. Subject has toxicity from previous anti-cancer therapy that has not recovered to Grade ≤1 prior to enrollment (except for non-clinically significant toxicities, e.g., alopecia, vitiligo). Subjects with existing pneumonitis as a result of radiation are not excluded; however, subjects cannot be oxygen dependent. Subjects with Grade 2 toxicities that are deemed stable or irreversible (e.g. peripheral neuropathy) can be enrolled on a case-by-case basis with prior consultation and agreement with the Sponsor Study Physician.
4. Subject has a history of allergic reactions attributed to compounds of similar chemical or biologic composition to cyclophosphamide, fludarabine, or other agents used in the study.
5. Subject has a history of chronic or recurrent (within the last year prior to enrollment) severe autoimmune or active immune-mediated disease requiring steroids or other immunosuppressive treatments.
6. Subject has symptomatic CNS metastases. Subjects with prior history of symptomatic CNS metastasis must have received treatment (i.e., stereotactic radiosurgery (SRS), whole brain radiotherapy (WBRT) or surgery) and be neurologically stable, not requiring anti-seizure medications and off steroids for at least 14 days prior to lymphodepletion. Subject who has asymptomatic CNS metastatic disease without associated edema, shift, requirement for steroids or therapeutic anti-seizure medications are eligible. Medications for seizure prophylaxis are permitted. If such a subject receives SRS or WBRT, a minimum period of 2 weeks needs to lapse between the therapy and lymphodepletion. Subjects with leptomeningeal disease or carcinomatous meningitis are NOT eligible.
7. Subject has other active malignancy besides NSCLC within 3 years prior to Screening (prior to leukapheresis and prior to lymphodepletion).
   Exceptions: adequately treated malignancies not likely to require therapy (e.g. completely resected non-melanomatous skin carcinoma or successfully treated in situ carcinoma). Subjects must be in complete remission from prior malignancy in order to be eligible to enter the study.
8. Subject has ECG showing clinically significant abnormality at Screening or showing an average QTc interval ≥450 msec in males and ≥470 msec in females (≥480 msec for subjects with Bundle Branch Block over 2 consecutive ECGs).

9. Subject has 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 Class >1; uncontrolled clinically significant arrhythmia in last 6 months; acute coronary syndrome (angina or myocardial infarction) in last 6 months; history (family or subject) of congenital Long QT Syndrome or history of Torsade de Pointes;
   - Inadequate pulmonary function with mechanical parameters <40% predicted (FEV1, FVC, TLC, DLCO);
   - Current uncontrolled hypertension despite optimal medical therapy.
   - History of stroke or central nervous system bleeding, transient ischemic attack (TIA) or reversible ischemic neurologic deficit (RIND) within last 6 months.
   - Interstitial lung disease (subjects with existing pneumonitis as a result of radiation are not excluded; however, subjects cannot be oxygen dependent).
10. Subjects who in the opinion of the Investigator will be unlikely to fully comply with protocol requirements.
11. Subject has active infection with HIV, HBV, HCV, or HTLV as minimally defined below:
    - Positive serology for HIV;
    - Active hepatitis B infection as determined by 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 chemotherapy and continued for 6 months (Section 8.2.4);
      - Subjects who are hepatitis B surface antigen negative and hepatitis B core antibody positive and have detectable hepatitis B DNA are excluded.
    - Active hepatitis C infection as determined by hepatitis C RNA;
      - A subject who is 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.
12. Subject is pregnant or breastfeeding.

4.3. Additional Eligibility Criteria (Prior to Lymphodepleting Chemotherapy)

Prior to lymphodepleting chemotherapy, all subjects must meet all the inclusion and exclusion in Section 4.2 as assessed at the baseline visit and the following inclusion criterion:

1. Subject has received at least one prior line of therapy and has measurable disease according to RECIST v1.1 criteria (Eisenhauer, 2009).

Subject may have received chemotherapy or PD-1 or PDL-1 inhibitors. Subjects with known EGFR mutations or ALK or ROS1 gene rearrangements have failed (PD or unacceptable toxicity) at least one prior EGFR or ALK or ROS1 tyrosine kinase inhibitor (TKI) where indicated, respectively. There is no limit on lines of prior anti-cancer therapy.

2. Subject has an anticipated life expectancy >3 months prior to lymphodepletion.

Furthermore and prior to lymphodepleting chemotherapy, a subject meeting the following exclusion criteria is not eligible for participation in the study:

1. Subject has received:
   - Cytotoxic chemotherapy within 3 weeks prior to lymphodepleting chemotherapy;
   - Immune therapy (including monoclonal antibody therapy, checkpoint inhibitors) or biological therapy within 2 weeks prior to lymphodepleting chemotherapy;
   - Corticosteroids or any other immunosuppressive therapy within 2 weeks prior to lymphodepleting chemotherapy;
     NOTE: A brief course of oral corticosteroids limited to less than 7 days is not exclusionary if completed 2 weeks prior to lymphodepleting chemotherapy; a recent or current use of inhaled or topical steroids is not exclusionary. Other exceptions are also provided for specific systemic steroid use in Section 6.1;
   - Experimental anti-cancer vaccine within 2 months prior to lymphodepletion in the absence of response or in the opinion of the Investigator is responding to an experimental vaccine given within 6 months prior to lymphodepletion;
   - Major surgery within 4 weeks prior to lymphodepleting chemotherapy; subjects must have recovered from any surgical-related toxicities in the opinion of the Investigator;
   - Radiotherapy that involves the lung (V20 exceeding 30% lung volume) or mean heart dose of >20Gy within 3 months prior to lymphodepleting chemotherapy; for a lesser dose of radiation exposure to lung/mediastinum than stated, administered within 4 weeks prior to lymphodepletion. Electron beam radiotherapy to superficial structures in the chest is permitted. Radiation to other vital organs (e.g., liver, spleen, GI tract) within 2 weeks prior to lymphodepletion. Radiotherapy to the pelvis within 4 weeks.
     NOTE: there is no washout period for palliative radiation to non-target organs other than the lung and mediastinum. If radiation was to an intended target lesion within 3 months of baseline imaging studies, and the lesion is progressing within this time frame it may be considered as a target lesion after review and discussion with the Sponsor.
   - Note: there is no required wash out period for small molecules or tyrosine kinase inhibitors prior to lymphodepletion.

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

Prior to receipt of a second T-cell infusion, all subjects must remain eligible to receive manufactured T-cell product as defined in Section 4.2 and Section 4.3 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.
2. A second T cell infusion is recommended by the Investigator.
3. Subject has a new tumor biopsy confirming MAGE-A10 expression.
4. Subject has voluntarily agreed to receive a second T-cell infusion by giving written informed consent.
5. Subject has toxicity from first T-cell infusion that resolved to Grade ≤1.
6. Manufactured T-cell product must be 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 with any Grade 4 CRS or clinically life-threatening (Grade 4) AEs deemed at least possibly related to the MAGE-A10^{c796}T cell product by the Investigator and study Sponsor reported during the first T-cell infusion.

4.5. Interventional and LTFU Phases

A subject will be considered to have ended the Interventional Phase of the study when he/she has received the T cell infusion and subsequently has PD, has died prior to PD or withdrawn. Subjects that have PD or withdraw prior to Week 12, will be considered to have ended the Interventional Phase of the study only after they have been followed up for safety only for at least 12 weeks (up to and including Week 12) according to the Schedule of Procedures (Table 6). Once progression is established, no further efficacy assessments will be collected, other than overall survival. When a follow-up confirmatory scan is required to confirm progression, then the Interventional Phase will be considered to have completed after that confirmatory scan. If there is unequivocal evidence of PD and/ or the need for an alternate anti-cancer treatment a confirmatory scan is not required.

After the Interventional Phase of the study, subjects will continue in the LTFU Phase to continue monitoring for the emergence of LTFU AEs during the 15 years post-infusion in accordance with FDA and EMA regulations (EMEA, 2009; FDA, 2006a), and as described in Section 7.4.8 and Section 9.4. A subject will be considered to have ended the study when he/she has been followed for 15 years from time of last T cell infusion or discontinued the study for any reason. The study will be considered complete once the last subject has been

followed for 15 years from time of last T cell infusion or has discontinued from the study for any reason.

4.6. 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. 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'. Date of last contact (any method) with the subject will be recorded.

Results of any evaluations and observations performed prior to withdrawal of consent, together with a description of the reasons for study withdrawal, must be recorded in the medical records and electronic Case Report Forms (eCRF).

4.6.1. Ending the Interventional Phase

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

- Disease progression per RECIST
- Clinical progression
- Died
- Unable/unwilling to comply with study requirements
- Withdrawal of consent
- Investigator decision
- Adverse Event
- Lost to follow-up
- Pregnancy (see Section 9.7)
- 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 the LTFU Phase for observation of delayed adverse events as described in Section 7.4.8. 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 9.4.

Subjects should not receive lymphodepleting chemotherapy until the cell product has met all release criteria and is received 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 SAEs have resolved to at least Grade 1 or baseline, whichever is longer or until no further improvement can be expected.

4.6.2. Discontinuation from the study

Reasons for discontinuation of a subject from the study include:

- Completed 15 years follow up after last T cell infusion
- Died
- Unable/unwilling to comply with study requirements
- Withdrawal of consent
- Investigator decision
- Adverse Event
- Lost to follow-up
- Pregnancy
- Termination of the study by the Sponsor.
- Did not consent to LTFU

4.7. Consideration for Temporary Suspension of Enrollment

In addition to the periodic safety reviews by the SRC (refer to Section 10.3 for details of the SRC), 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 anti-tumor 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 probably related to the MAGE-A10^{c796}T cell product by the Investigator and the Sponsor; or
- Two or more Grade 4 autoimmune events deemed probably or definitely related to the MAGE-A10^{c796}T cell 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 10.1 on Monitoring and Management of RCL).
  - Positive biological RCL - all MAGE-A10^{c796}T cell infusions are halted (refer to Section 10.2).

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

5. STUDY TREATMENTS

5.1. Leukapheresis.

Subjects who complete screening procedures and meet all eligibility criteria defined in Section 4.2 will be eligible to undergo leukapheresis to obtain starting material for the manufacture of autologous MAGE-A10^{c796}T. Prior to leukapheresis, an absolute lymphocyte count of ≥0.5 x 10^9/L and the CD3 count ≥200/µL is recommended.

For collection of starting material, a large-volume non-mobilized peripheral blood mononuclear cell (PBMC) collection should be performed according to institutional standard procedures. 2-3 blood-volumes should be processed with a goal of collecting 1.0 x 10^8 PBMC/kg body weight, and a minimum of 1.5x10^7 PBMC/kg. In cases where the minimum number of PBMCs are not collected or the T cells are not able to be infused back to the subject, a second leukapheresis may be performed. Citrate anticoagulant should be used. Prophylaxis and treatment (e.g. $CaCl_2$ or $MgSO_4$) for adverse effects of the citrate anticoagulant may be used at the discretion of the Investigator. The collected leukapheresis product will then be transported for manufacture as detailed in the Apheresis and T-cell Manual.

Once MAGE-A10^{c796}T cell product has been manufactured and received at the site, eligible subjects will proceed to have lymphodepleting chemotherapy and infusion of IP as detailed in Section 5.2 and Section 5.3, respectively.

5.2. Lymphodepleting Chemotherapy

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

When the MAGE-A10^{c796}T cells have completed manufacture, have fulfilled release criteria, and are available for infusion at the site, fludarabine and cyclophosphamide will be administered as lymphodepleting chemotherapy as described in Table 3,Table 4, and Table 5.

Recommended prophylaxis and supportive medication apply to all Cell Dose Groups.

Cyclophosphamide and fludarabine will be supplied by the pharmacy of the participating Institution.

Table 3: Lymphodepleting Chemotherapy Treatment Regimen for ADP-0022-003 Group 1a

Lymphodepleting chemotherapy					**Recommended prophylaxis and supportive medication**
Day	**Drug**	**Dose**	**Route**	**Administration[1]**	**Infection:** on admission for lymphodepleting chemotherapy, commence anti-microbial and anti-fungal prophylaxis as recommended in Section 8.2 or in line with institutional standard practice. **Hydration:** ensure adequate hydration and antiemetic provision prior to commencing cyclophosphamide infusions Steroids may be used as anti-emetics for cyclophosphamide but must be discontinued no later than Day -3. **Mesna:** may be given to prevent urotoxicity per institutional guidelines or as recommended in Section 5.2.2 **G-CSF:** recommend starting 24 hours after the last dose of lymphodepleting chemotherapy until resolution of neutropenia in accordance with ASCO guidelines (Smith, 2015) or institutional practice (refer to Section 8.9.1)[3].
-7	**Cyclophosphamide**	1800 mg/m^2	IV	in 100 – 250ml 0.9% NaCl over 1 hour	
-6	**Cyclophosphamide**	1800 mg/m^2	IV	in 100 – 250ml 0.9% NaCl over 1 hour	
-5	start **G-CSF**[3]				
-4					
-3					
-2					
-1					
1	**MAGE-A10^{c796}T infusion**[2]				

Abbreviations: ASCO = American Society of Clinical Oncology; IV = intravenous; NaCl = sodium chloride; G-CSF = granulocyte-colony stimulating factor

1 Or per institutional guidelines

2 Administration of MAGE-A10^{c796}T infusion is described in Section 5.3

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 24 hours after the last chemotherapy administered

Table 4: Lymphodepleting Chemotherapy Treatment Regimen for ADP-0022-003 for Group 2

Lymphodepleting chemotherapy					**Recommended prophylaxis and supportive medication**
Day	**Drug**	**Dose**	**Route**	**Administration[1]**	**Infection:** on admission for lymphodepleting chemotherapy, commence anti-microbial and anti-fungal prophylaxis as recommended in Section 8.2 or in line with institutional standard practice. **Hydration:** ensure adequate hydration and antiemetic provision prior to commencing cyclophosphamide infusions. Steroids may be used as anti-emetics for cyclophosphamide but must be discontinued no later than Day -3 **Mesna:** may be given to prevent urotoxicity per institutional guidelines or as recommended in Section 5.2.2 **G-CSF:** recommend starting 24 hours after the last dose of lymphodepleting chemotherapy until resolution of neutropenia in accordance with ASCO guidelines (Smith, 2015) or institutional practice (refer to Section 8.9.1)[5].
-7	**Fludarabine[2]**	30 mg/m^2	IV	in 50 - 100ml 0.9% NaCl over 30 mins[3]	
	Cyclophosphamide	600 mg/m^2	IV	in 100 – 250ml 0.9% NaCl over 1 hour	
-6	**Fludarabine[2]**	30 mg/m^2	IV	in 50 - 100ml 0.9% NaCl over 30 mins[3]	
	Cyclophosphamide	600 mg/m^2	IV	in 100 – 250ml 0.9% NaCl over 1 hour	
-5	**Fludarabine[2]**	30 mg/m^2	IV	in 50 - 100ml 0.9% NaCl over 30 mins[3]	
	Cyclophosphamide	600 mg/m^2	IV	in 100 – 250ml 0.9% NaCl over 1 hour	
-4	start **G-CSF[5]**				
-3					
-2					
-1					
1	**MAGE-A10^{c796}T infusion[4]**				

Abbreviations: ASCO = American Society of Clinical Oncology; IV = intravenous; NaCl = sodium chloride; G-CSF = granulocyte-colony stimulating factor

1 Or per institutional guidelines
2 Fludarabine dose will be adjusted in renal impairment as described in Section 5.2.1
3 Concentration ≤1mg/mL
4 Administration of MAGE-A10^{c796}T infusion is described in Section 5.3
5 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 24 hours after the last chemotherapy administered

Table 5: Lymphodepleting Chemotherapy Treatment Regimen for ADP-0022-003 for Group 3 and Expansion Group

Lymphodepleting chemotherapy					**Recommended prophylaxis and supportive medication**
Day	**Drug**	**Dose**	**Route**	**Administration[1]**	**Infection:** on admission for lymphodepleting chemotherapy, commence anti-microbial and anti-fungal prophylaxis as recommended in Section 8.2 or in line with institutional standard practice. **Hydration:** ensure adequate hydration and antiemetic provision prior to commencing cyclophosphamide infusions. Steroids may be used as anti-emetics for cyclophosphamide but must be discontinued no later than Day -3 **Mesna:** may be given to prevent urotoxicity per institutional guidelines or as recommended in Section 5.2.2 **G-CSF:** Start 24 hours after the last dose of lymphodepleting chemotherapy until resolution of neutropenia in accordance with ASCO guidelines (Smith, 2015) or institutional practice (refer to Section 8.9.1)[5].
-7	**Fludarabine[2]**	30 mg/m^2	IV	in 50 - 100ml 0.9% NaCl over 30 mins[3]	
	Cyclophosphamide	600 mg/m^2	IV	in 100 – 250ml 0.9% NaCl over 1 hour	
-6	**Fludarabine[2]**	30 mg/m^2	IV	in 50 - 100ml 0.9% NaCl over 30 mins[3]	
	Cyclophosphamide	600 mg/m^2	IV	in 100 – 250ml 0.9% NaCl over 1 hour	
-5	**Fludarabine[2]**	30 mg/m^2	IV	in 50 - 100ml 0.9% NaCl over 30 mins[3]	
	Cyclophosphamide	600 mg/m^2	IV	in 100 – 250ml 0.9% NaCl over 1 hour	
-4	**Fludarabine[2]**	30 mg/m^2	IV	in 50 - 100ml 0.9% NaCl over 30 mins[3]	
-3	start **G-CSF[5]**				
-2					
-1					
1	**MAGE-A10^{c796}T infusion[4]**				

Abbreviations: ASCO = American Society of Clinical Oncology; IV = intravenous; NaCl = sodium chloride; G-CSF = granulocyte-colony stimulating factor

1 Or per institutional guidelines
2 Fludarabine dose will be adjusted in renal impairment as described in Section 5.2.1
3 Concentration ≤1mg/mL
4 Administration of MAGE-A10^{c796}T infusion is described in Section 5.3
5 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 24 hours after the last chemotherapy administered

5.2.1. 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
60 – 79 mL/min	20 mg/m^2

5.2.2. Mesna

Mesna should be administered per institutional guidelines or as recommended below:

- 20% of cyclophosphamide dose (120 mg/m^2) x 4 doses at times 0 (start of cyclophosphamide infusion) and then 3 hours, 6 hours and 9 hours after the start of each cyclophosphamide infusion.

5.3. T Cell Infusion

The autologous T-cells transduced with lentivirus encoding enhanced TCR specific for cancer-testis antigen MAGE-A10 is the investigational product in this study.

This trial will evaluate 3 cell dose levels of MAGE-A10^{c796}T and will treat subjects using a modified 3+3 dose escalation study design as outlined in Table 1.

Subjects will receive a single dose of MAGE-A10^{c796}T after completing the lymphodepleting chemotherapy. This is considered Day 1 and all procedures and assessments to be performed are listed in the Schedule of Procedures (Table 6).

5.3.1. Premedication

Thirty to sixty (30-60) minutes prior to T cell infusion, subjects will be pre-medicated against potential infusion reactions with anti-histamine and acetaminophen (paracetamol) as per institutional standards. **NOTE:** Steroids must not be administered as premedication for T cell infusion because they are lymphotoxic and inhibitory to the T-cell product.

5.3.2. T Cell Infusion

On Day 1, the subject will receive thawed MAGE-A10^{c796}T by intravenous infusion. 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 participating center's blood bank procedures.

MAGE-A10^{c796}T 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 3-5 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 in a water bath 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 2-8°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 of each bag 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 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 PI and Sponsor should be notified and the cells should not be infused.

The cell product must not be washed or otherwise processed. MAGE-A10^{c796}T will be administered using a dual spike infusion set by gravity over 15-45 minutes in the absence of infusion reaction. It is recommended that the cells are 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 - 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 MAGE-A10^{c796}T, the main line should be closed and approximately 50ml 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 (refer to Section 8.1). Steroid treatment should be avoided unless medically required. In the event a subject develops 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.

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. The timing of all assessments post-infusion will be calculated with reference to the T-cell infusion date. Subjects who have undergone leukapheresis but do not receive the T-cell infusion will be replaced. Cytopenias alone should not be a reason to delay T-cell infusion unless complications are present.

Vital signs will be recorded prior to the infusion, and at 5, 15, and 30 minutes, 1, 1.5, 2 and 4 hours after the infusion has started.

5.4. Second T Cell Infusions (Interventional Phase 2)

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-A10 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 4.4 prior to receiving a second infusion.

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 9 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 Schedule of Procedures (Table 6). However, no other clinical assessments or procedures are required until the subject is consented for the Interventional Phase 2.

Some subjects may need to have another leukapheresis. Prior to Screening subjects for the Interventional Phase 2 (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. Table 17 provides the Schedule of Procedures for those subjects who will not require another leukapheresis collection of cells. For subjects who do require another leukapheresis, please follow the clinical procedures and assessments noted in the Screening phase, Leukapheresis, and Baseline visits as outlined in Table 6 with the exception of the following procedures, which are not required:

- Demographics
- Tobacco use
- Cardiac troponin I or T
- Tumor biopsy at Baseline

NOTE: If a fresh biopsy was taken to confirm continued expression of MAGE-A10 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 Interventional Phase 2. 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.

These subjects will then continue to follow the clinical assessment and procedures outlined in Table 17from the Lymphodepleting Chemotherapy visit onward.

Subjects that qualify for a second infusion will receive the lymphodepleting chemotherapy regimen and T cell infusion at the doses deemed safe and as defined in Table 1.

6. CONCOMITANT MEDICATION AND TREATMENT

6.1. Prohibited Concomitant Medication and Treatment

The following treatments are prohibited during the Interventional Phase of the study: non-protocol chemotherapy, immune therapy, biological therapy (including targeted therapies with TKIs or monoclonal antibodies), or investigational anti-cancer therapy. Subjects should also not undergo other anti-cancer locoregional therapies such as surgical resection or non-palliative radiation. Subjects should not require these therapies before confirmation of PD, and if used, will be discontinued from the Interventional phase (as long as subject is 12 weeks post T cell infusion) and will continue in the LTFU Phase and will not be eligible for a second T cell infusion.

Refer to Section 4.2 and Section 4.3 for details of washout and excluded treatments prior to leukapheresis and lymphodepleting chemotherapy, respectively.

The use of systemic steroids may abrogate the effects of the T cell therapy and; therefore, use is discouraged unless required to manage CRS (refer to Section 8.5 for CRS management) or other significant immune-mediated AEs. According to local standard of care or American Society of Clinical Oncology (ASCO) guidelines (Basch, 2010), steroids may be used as anti-emetics before cyclophosphamide but must be discontinued no later than 3 days prior to infusion of the IP. 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 is acceptable provided that the subject continues to meet eligibility criteria as per sections 41.2 and 4.3. Topical steroids for cutaneous application and inhaled steroidal treatments are permitted.

6.2. Permitted Concomitant Medication and Treatment

Lesion sites previously requiring radiotherapy should be recorded prior to lymphodepleting chemotherapy. Palliative radiation for pain relief to non-measurable lesions or non-target lesions present at Baseline, in organs other than the chest, is permitted during the study. If lesion sites require radiotherapy after the T cell infusion, it should be evaluated as to whether that indicates PD.

Other treatment that the Investigator considers necessary for a subject's welfare may be administered during the Interventional Phase of 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 member of the subject's household), consult an Infectious Disease specialist or a guidance such as the Centers for Disease Control and Prevention's Clinical Practice Guideline for Vaccination of the Immunocompromised Host.

All concomitant medications, including prescription, over-the-counter medications, and herbal remedies, will be recorded, including dose and frequency.

The following will be recorded on the appropriate eCRF pages:

- All prescription and non-prescription medication, vitamins, herbal and nutritional supplements taken by the subject during the 30 days prior to Screening will be recorded at the Screening Phase visit.
- All prior anti-cancer treatments taken by the subject must be recorded regardless of time.
- All concomitant medications taken by the subject while in the Interventional Phase.
  - Use of any mutagenic agents or investigational agents must be reported

Any changes to concomitant medication regimens should be recorded throughout the study in the eCRF.

7. SCHEDULE OF ASSESSMENTS AND PROCEDURES

The Schedule of Procedures is provided in Table 6 for the Interventional Phase Infusion 1 of the study and in Table 7 for the LTFU phase of the study. The Schedule of Procedures for the Interventional Phase Infusion 2 is provided in Table 17. After the Interventional Phase, subjects continue in the LTFU Phase. If a subject ends the Interventional Phase within three months after receiving T-cells, the following assessments will be performed through Week 12 according to Table 6:

Concomitant medications, Adverse Events, Hematology, Chemistry, and CMV PCR and VSV-G DNA (RCL).

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), in this study (ADP-0022-003), and in the LTFU Phase. Refer to the SPM for further details on assignment of Subject ID.

Study procedures performed as part of standard of care (laboratory assessments, radiologic imaging, including cardiac assessment) prior to signing informed consent can be used for Screening if they were performed within the time period prior to leukapheresis as noted in Table 6.

7.1. HLA and Antigen Screening (to be conducted in Screening Protocol, ADP-0000-001)

Subjects 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 meets the HLA eligibility criteria, and has a MAGE-A10 positive tumor prior to conducting the screening procedures in this study.

7.2. Schedule of Procedures

Table 6: Schedule of Procedures (Interventional Phase Infusion 1)

	Screening Phase[1]	Interventional Phase Infusion 1																									Completion/ Withdrawal[5]
		Leukapheresis	Baseline	Lymphodepleting Chemotherapy[2]				T-cell infusion[3]	Post-T-cell Infusion																		
Day (D) / Week (W)	**- 28 D[4] of Leukapheresis**		**D -14 to -8**	**D -7**	**D -6**	**D -5**	**D -4**	**D1**	**D 2**	**D 3**	**D 4**	**D 5**	**D 8**	**D 10 & 12**	**W 2**	**W 3**	**W 4**	**W 5**	**W 6**	**W 8**	**W 10**	**W 12**	**W 16**	**W 24**	**Every 3 Mos Until Yr 2.**	**Every 6 Mos Thereafter**	
Visit Window		**n/a**	**n/a**	**n/a**	**n/a**	**n/a**	**n/a**	**n/a**	**±1 day**						**±3 days**					**±7 days**					**±14 days**	**±3 mos**	**n/a**
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14/15	16	17	18	19	20	21	22	23	24	25	26-31	32+	
Clinical Assessments and Procedures[6] (refer to Section 7.4 for details)																											
Informed Consent[7]	X_{EDC}																										
Demographics	X_{EDC}																										
Inclusion/ Exclusion	X_{EDC}[8]		X[9]																								

	Screen-ing Phase[1]	Interventional Phase Infusion 1																								Compl etion/ Withdr awal[5]
		Leuka-pheresis	Base-line	Lymphodepleting Chemotherapy[2]				T-cell infusion[3]	Post-T-cell Infusion																	
Day (D) / Week (W)	**- 28 D[4] of Leuka-pheresis**		**D -14 to -8**	**D -7**	**D -6**	**D -5**	**D -4**	**D1**	**D 2**	**D 3**	**D 4**	**D 5**	**D 8**	**D 10 & 12**	**W 2**	**W 3**	**W 4**	**W 5**	**W 6**	**W 8**	**W 10**	**W 12**	**W 16**	**W 24**	**Every 3 Mos Until Yr 2.**	**Every 6 Mos There-after**	
Visit Window		**n/a**	**n/a**	**n/a**	**n/a**	**n/a**	**n/a**	**n/a**	**±1 day**						**±3 days**					**±7 days**					**±14 days**	**±3 mos**	**n/a**
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14/15	16	17	18	19	20	21	22	23	24	25	26-31	32+	
Medical History[10], and Tobacco Use	X																										
Physical Exam	X		X					X					X		X									X	X	X	
Prior/Concomi-tant Medications[11]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECOG	X		X					X					X		X	X	X		X	X		X	X	X	X	X	X
Vital Signs / Height/ Weight[12]	X		X					X[13]	X	X	X	X	X		X												X
ECG[32]	X		X					X	X		X		X														

	Screening Phase[1]	Interventional Phase Infusion 1																								Completion/ Withdrawal[5]
		Leukapheresis	Baseline	Lymphodepleting Chemotherapy[2]				T-cell infusion[3]	Post-T-cell Infusion																	
Day (D) / Week (W)	**- 28 D[4] of Leukapheresis**		**D -14 to -8**	**D -7**	**D -6**	**D -5**	**D -4**	**D1**	**D 2**	**D 3**	**D 4**	**D 5**	**D 8**	**D 10 & 12**	**W 2**	**W 3**	**W 4**	**W 5**	**W 6**	**W 8**	**W 10**	**W 12**	**W 16**	**W 24**	**Every 3 Mos Until Yr 2.**	**Every 6 Mos Thereafter**	
Visit Window		**n/a**	**n/a**	**n/a**	**n/a**	**n/a**	**n/a**	**n/a**	**±1 day**						**±3 days**					**±7 days**					**±14 days**	**±3 mos**	**n/a**
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14/15	16	17	18	19	20	21	22	23	24	25	26-31	32+	
ECHO/MUGA	**X$_{EDC}$**[4]																										
CT / MRI[14]			X														X			X		X		X	X	X	X
Brain MRI[14]	X		X																								
Chest X-ray			X																								
PFTs[15]	**X$_{EDC}$**																										
Telemetry monitoring								X[33]																			
CARTOX-10								X[34]	X	X	X	X	X														

	Screen-ing Phase[1]	Interventional Phase Infusion 1																								Completion/ Withdrawal[5]
		Leuka-pheresis	Base-line	Lymphodepleting Chemotherapy[2]				T-cell infusion[3]	Post-T-cell Infusion																	
Day (D) / Week (W)	**- 28 D[4] of Leuka-pheresis**		**D -14 to -8**	**D -7**	**D -6**	**D -5**	**D -4**	**D1**	**D 2**	**D 3**	**D 4**	**D 5**	**D 8**	**D 10 & 12**	**W 2**	**W 3**	**W 4**	**W 5**	**W 6**	**W 8**	**W 10**	**W 12**	**W 16**	**W 24**	**Every 3 Mos Until Yr 2.**	**Every 6 Mos There-after**	
Visit Window		**n/a**	**n/a**	**n/a**	**n/a**	**n/a**	**n/a**	**n/a**	**±1 day**						**±3 days**					**±7 days**					**±14 days**	**±3 mos**	**n/a**
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14/15	16	17	18	19	20	21	22	23	24	25	26-31	32+	
Lymphocyte Subset (CD3/CD4/CD8)[31]	X_{EDC}																										
Hematology	X_{EDC}[4]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chemistry	X[4]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X		X	X	X	X	X	X
Amylase, Lipase			X																								
Coagulation Tests	X[4]		X																								
Pregnancy Test[16]	X		X																								

	Screen-ing Phase[1]	Interventional Phase Infusion 1																								Completion/ Withdrawal[5]
		Leuka-pheresis	Base-line	Lymphodepleting Chemotherapy[2]				T-cell infusion[3]	Post-T-cell Infusion																	
Day (D) / Week (W)	- 28 D[4] of Leuka-pheresis		D -14 to -8	D -7	D -6	D -5	D -4	D1	D 2	D 3	D 4	D 5	D 8	D 10 & 12	W 2	W 3	W 4	W 5	W 6	W 8	W 10	W 12	W 16	W 24	Every 3 Mos Until Yr 2.	Every 6 Mos There-after	
Visit Window		n/a	n/a	n/a	n/a	n/a	n/a	n/a	±1 day						±3 days					±7 days					±14 days	±3 mos	n/a
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14/15	16	17	18	19	20	21	22	23	24	25	26-31	32+	
Urinalysis	X[4]		X																								
Infectious disease markers[17]	X_{EDC}																										
CMV IgG and PCR[18]			X					X							X		X		X	X							
TSH with free T4[19]			X																								
CRP[20]			X					X			X		X		X		X										
Uric acid			X					X												`							
GFR or 24h urine[21]	X		X																								

	Screening Phase[1]	Interventional Phase Infusion 1																									Completion/ Withdrawal[5]
		Leukapheresis	Baseline	Lymphodepleting Chemotherapy[2]				T-cell infusion[3]	Post-T-cell Infusion																		
Day (D) / Week (W)	**- 28 D[4] of Leukapheresis**		**D -14 to -8**	**D -7**	**D -6**	**D -5**	**D -4**	**D1**	**D 2**	**D 3**	**D 4**	**D 5**	**D 8**	**D 10 & 12**	**W 2**	**W 3**	**W 4**	**W 5**	**W 6**	**W 8**	**W 10**	**W 12**	**W 16**	**W 24**	**Every 3 Mos Until Yr 2.**	**Every 6 Mos Thereafter**	
Visit Window		**n/a**	**n/a**	**n/a**	**n/a**	**n/a**	**n/a**	**n/a**	**±1 day**						**±3 days**					**±7 days**					**±14 days**	**±3 mos**	**n/a**
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14/15	16	17	18	19	20	21	22	23	24	25	26-31	32+	
Troponin (cTnI or cTnT)[22]			X						X		X		X		X												
Adverse Events[23]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Overall survival	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vector Copies (Persistence for Safety)[24]			X																					X		X[24]	
VSV-G DNA (RCL)[25]			X																			X		X		X[25]	

	Screening Phase[1]	Interventional Phase Infusion 1																										Completion/ Withdrawal[5]
		Leukapheresis	Baseline	Lymphodepleting Chemotherapy[2]				T-cell infusion[3]	Post-T-cell Infusion																			
Day (D) / Week (W)	**- 28 D[4] of Leukapheresis**		**D -14 to -8**	**D -7**	**D -6**	**D -5**	**D -4**	**D1**	**D 2**	**D 3**	**D 4**	**D 5**	**D 8**	**D 10 & 12**	**W 2**	**W 3**	**W 4**	**W 5**	**W 6**	**W 8**	**W 10**	**W 12**	**W 16**	**W 24**	**Every 3 Mos Until Yr 2.**	**Every 6 Mos Thereafter**	
Visit Window		**n/a**	**n/a**	**n/a**	**n/a**	**n/a**	**n/a**	**n/a**	**±1 day**						**±3 days**					**±7 days**					**±14 days**	**±3 mos**	**n/a**
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14/15	16	17	18	19	20	21	22	23	24	25	26-31	32+	
Leukapheresis, Lymphodepleting Chemotherapy & Investigational Product Administration																											
Leukapheresis		X																									
Fludarabine[26]				X	X	X	X																				
Cyclophos-phamide[26]				X	X	X																					
MAGE-A10^{c796}T								X																			
Correlative Studies and Research Assessments (refer to Section 7.5 for details)																											
Tumor biopsy[28]			X[28a]													X											X

	Screening Phase[1]	Interventional Phase Infusion 1																									Completion/ Withdrawal[5]
		Leukapheresis	Baseline	Lymphodepleting Chemotherapy[2]				T-cell infusion[3]	Post-T-cell Infusion																		
Day (D) / Week (W)	- 28 D[4] of Leukapheresis		D -14 to -8	D -7	D -6	D -5	D -4	D1	D 2	D 3	D 4	D 5	D 8	D 10 & 12	W 2	W 3	W 4	W 5	W 6	W 8	W 10	W 12	W 16	W 24	Every 3 Mos Until Yr 2.	Every 6 Mos Thereafter	
Visit Window		n/a	n/a	n/a	n/a	n/a	n/a	n/a	±1 day						±3 days					±7 days					±14 days	±3 mos	n/a
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14/15	16	17	18	19	20	21	22	23	24	25	26-31	32+	
[redacted]																											
[redacted]																											
[redacted]																											

	Screening Phase[1]	Interventional Phase Infusion 1																								Completion/ Withdrawal[5]
		Leukapheresis	Baseline	Lymphodepleting Chemotherapy[2]				T-cell infusion[3]	Post-T-cell Infusion																	
Day (D) / Week (W)	- 28 D[4] of Leukapheresis		D -14 to -8	D -7	D -6	D -5	D -4	D1	D2	D 3	D 4	D 5	D 8	D 10 & 12	W 2	W 3	W 4	W 5	W 6	W 8	W 10	W 12	W 16	W 24	Every 3 Mos Until Yr 2.	Every 6 Mos Thereafter	
Visit Window		n/a	n/a	n/a	n/a	n/a	n/a	n/a	±1 day						±3 days					±7 days					±14 days	±3 mos	n/a
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14/15	16	17	18	19	20	21	22	23	24	25	26-31	32+	
Serum for Cytokine [redacted][20]			X					X	X	X	X	X	X		X	X	X			X		X		X	X		
Vector Copies (Persistence) for Research									X		X		X		X		X			X		X			X		X

Abbreviations: CMV = cytomegalovirus; CRP = C-reactive protein; CRS = cytokine release syndrome; CT = computerized tomography; cTnI and cTnT – cardiac-specific troponin I and cardiac-specific troponin T; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; EDC = electronic data capture; FPCP = female patient of childbearing potential; GFR = glomerular filtration rate; MRI = magnetic resonance imaging; MUGA = multigated acquisition scan; n/a=not applicable; PCR = polymerase chain reaction; PFT = pulmonary function test; RCL = replication competent lentivirus; TSH = thyroid-stimulating hormone; VSV-G =vesicular stomatitis virus G protein

1 Subjects must have completed screening under Screening Protocol, ADP-0000-001, and confirmed as HLA-A*02:01 and/or HLA-A*02:06 positive, HLA-A*02:05, HLA-B*15:01 and HLA-B*4601 negative, and have MAGE-A10 positive tumor prior to conducting the procedures in this visit. All clinical assessments and procedures in this visit must be performed as indicated and recorded in source documents; however, only those assessments/procedures indicated with bold **X$_{EDC}$** will be recorded in the EDC at this visit.

2 Refer to Section 5.2 for details on prophylaxis therapies, pre-medications, fludarabine dose adjustments according to renal function, and supportive treatments.

3 All samples will be collected and assessments performed prior to T-cell infusion, unless otherwise specified.

4 All clinical assessments required at the Screening visit must be performed within 28 days of leukapheresis, with the exception of lymphocyte subset (CD3/CD4/CD8), hematology, chemistry, coagulation and urinalysis which must be done within 7 days of leukapheresis. ECHO/MUGA, MRI/CT scan and laboratory assessments performed as standard of care prior to study consent will be acceptable as long as assessment is done within required time period before leukapheresis. ECG and ECHO/MUGA do not need to be repeated prior to lymphodepletion unless patient is symptomatic or has had therapy known to adversely affect cardiac function.

5 If a subject withdraws consent or ends the Interventional Phase Infusion 1, all procedures and assessments listed at this visit must be performed, unless done within the previous 30 days. Note - a tumor biopsy is still requested at progression or post progression confirmation (e.g. from an excisional surgery), irrespective of the previous biopsy occurring within the prior 30 days.

6 All clinical assessments and procedures must be performed as indicated; however, any clinical assessment or procedure can be performed if clinically indicated at any time

7 Written subject informed consent must be obtained prior to performing any assessment or procedures, unless otherwise specified.

8 Subjects must meet all eligibility prior to leukapheresis as specified in Section 4.2.

9 Subjects must continue to meet all eligibility criteria (Section 4.2) in addition to meeting those prior to lymphodepleting chemotherapy specified in Section 4.3.

10 Medical history will be recorded in the EDC at Screening; however, any changes in medical history must be recorded in source documents throughout the conduct of the study.

11 Includes all prescription, over-the-counter medications, and herbal remedies. Any use of mutagenic agents or investigational agents must also be reported.

12 Includes weight, temperature, blood pressure, pulse rate, respiratory rate, and oxygen saturation. Height will be collected at the Screening visit only.

13 Vital signs on day of T cell infusion should be taken pre-infusion, and at 5, 15 and 30 minutes, and 1, 1.5, 2, and 4 hours after the infusion has started

14 If a subject is found to have a tumor response or PD by imaging, a follow-up confirmation scan must be done no earlier than 4 weeks following the scan when response or PD first seen. A subject is not considered to have a response or PD until follow-up scan confirms the finding. If there is unequivocal evidence of PD and/ or the need for an alternate anti-cancer treatment a confirmatory scan is not required. Brain MRI is recommended at screening and required at baseline (within 1 month prior to lymphodepletion). If CNS metastases are detected at screening or baseline a brain MRI should be performed at all subsequent CT/MRI visits, and if clinically indicated. See Section 7.4.7.

15 Includes FEV1, FVC, TLC, and DLCO parameters to determine eligibility as described in Exclusion criterion #9.

16 FPCP must have a negative urine or serum pregnancy test.

17 Includes HIV, HBV, HCV, HTLV, EBV, and syphilis (spirochaete bacterium). Refer to Exclusion criterion #11 for details on required testing for eligibility. Testing for infectious disease markers is required only at Screening and does not need to be repeated at Baseline to satisfy eligibility criteria.

18 Only subjects who are CMV IgG seropositive at Baseline will continue to be monitored for CMV viremia by CMV DNA PCR post Baseline.

19 A free T4 test should be performed in subjects who have an abnormal TSH function test (high or low).

20 If CRS is suspected, cytokine and C-reactive protein levels should be measured approximately every other day until symptoms are improving or an alternative diagnosis is confirmed.

21 Creatinine clearance will be calculated using the Cockcroft-Gault Method or by 24-hour urine creatinine collection or by EDTA GFR measurement, or DTPA according to standard practice at the treating Institution.

Sites may use either cardiac troponin I or cardiac troponin T (cTnI or cTnT) as long as the same assay is used consistently for the subject.
Adverse events should be reported as noted in Section 9.1.
Persistence for safety of gene modified cells in subjects will be monitored at Baseline, Month 6, and 12 post-infusion, then every 6 months until 5 years post-infusion and annually from year 6-15 post infusion. If no gene modified cells are detected for 3 consecutive assessments post-infusion, and subject is ≥5 years post-infusion, then sample collection may stop.
RCL samples are collected at Baseline, Months 3, 6 and 12 post-infusion, then annually. If RCL tests are negative at all time points during the first year, then samples will be collected annually and archived for up to 15 years post infusion. However, if VSV-G DNA copies are detected at any time point in the first year post-infusion, refer to the safety monitoring procedures in Section 10.1.2.
Subjects treated in Cell Dose Group 1a will receive cyclophosphamide only on Day -7 and Day -6 as defined in Table 1
[redacted]
Core needle biopsies for research are at Baseline, week 3 (+ 5 weeks), and at or after confirmation of PD, with the exception of subjects for whom there is no safely accessible tumor tissue. 28a.) If a fresh biopsy was taken for MAGE-A10 confirmation screening in Screening Protocol, ADP-0000-001, and there is sufficient tumor sample left remaining, this sample may be used as the baseline sample. 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.
Liquid biopsy (Exosome/cfDNA) samples are collected at Baseline, Day 1 (infusion), Week 2, Week 4, Week 8 and completion withdrawal. Liquid biopsy samples are collected in addition to on-study biopsies requested, not in lieu of.
[redacted]
Lymphocyte subset is recommended but not required if sites cannot test this in their local laboratory.
Duplicate ECGs are required at screening only (prior to leukapheresis) as long as the subject remains asymptomatic and remains within parameters.
For subjects with known cardiac or pericardial tumor involvement at baseline, inpatient telemetry monitoring should be carried out for a minimum of seven days post MAGE-A10 infusion
CARTOX-10 assessment must be done prior to T-cell infusion on Day 1. Refer to Section 8.8 for further details including when additional assessments may be required.

Table 7: Schedule of Procedures (Long Term Follow-up Phase)

Time post-infusion											
	Year 1		**Year 2**		**Year 3**		**Year 4**		**Year 5**		**Years 6-15**
Months	6	12	18	24	30	36	42	48	54	60	Annually
Visit window	± 1 month										± 3 months
Safety Assessments											
New Medical History[1]	X	X	X	X	X	X	X	X	X	X	X
New mutagenic agents, other investigational agents or anti-cancer therapies[1]	X	X	X	X	X	X	X	X	X	X	X
LTFU Adverse Events[2]	X	X	X	X	X	X	X	X	X	X	X
Hematology	X	X	X	X	X	X	X	X	X	X	X[5]
Biochemistry	X	X	X	X	X	X	X	X	X	X	X[5]
VSV-G DNA (RCL)[3]	X	X		X		X		X		X	X
Vector Copies (Persistence)[4]	X	X	X	X	X	X	X	X	X	X	X[5]

1 New medical history/medications/chemotherapies

2 Adverse Event collection is limited to:
- New malignancies
- New incidence or exacerbation of a pre-existing neurologic 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 and 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 and/or hospitalization deemed related to gene modified cell therapy.

3 Samples for RCL (VSV-G copies) are collected as described in Section 10.1.1. If all RCL samples are negative in Year 1, samples will be collected and archived annually until 15 years post-infusion.

4 Samples for persistence are collected as described in Section 10.2.1.

5 Samples for persistence may be discontinued for subjects with 3 consecutive negative tests ≥5 years post-infusion. If persistence sampling is stopped hematology & biochemistry sampling can also be discontinued.

7.3. 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.

7.4. Clinical Assessments and Procedures

7.4.1. Medical History

A complete medical history (including demographics and tobacco use) will be recorded at Screening in the subject's medical record and eCRF.

7.4.2. Physical Examination and Measurement of Vital Signs

At Screening, subjects will undergo a physical examination including weight, height and measurement of their vital signs (temperature, pulse rate, respiratory rate, oxygen saturation, and blood pressure). The frequency of physical examination, weight and vital sign assessments at subsequent visits is specified in the Schedule of Procedures (Table 6). Vital sign measurements at 5, 15 and 30 minutes post infusion may have a ± 2 minute window. Vital sign measurements at 1, 1.5, 2 and 4 hours post infusion may have a ± 5 minute window.

7.4.3. Performance Status

At Screening, performance status will be measured using the ECOG performance scale (refer to Appendix 2). 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 the Schedule of Procedures (Table 6).

7.4.4. Clinical Safety Assessments

Subjects will be assessed for AEs throughout the study. AEs are to be graded by NCI CTCAE v4.0. All AEs must be recorded in the eCRF. Additionally, subjects will be monitored for RCL and persistence throughout the study as described in Section 10.1 and Section 10.2, respectively.

Details on assessing and reporting AEs and SAEs are described in Section 9.

7.4.5. Laboratory Assessments

All laboratory assessments will be performed locally at the site, and laboratory test reference ranges must be provided to Adaptimmune before the study initiates.

Female subjects of childbearing potential (FCBP) must have a negative pregnancy test at Screening and prior to starting lymphodepleting chemotherapy.

Refer to Schedule of Procedures (Table 6) for information regarding the frequency of these assessments and Appendix 3 for details on these local laboratory tests.

7.4.6. Cardiac and Other Assessments

All assessments will be performed locally at the site and will be conducted in order to monitor subject safety:

- An ECHO or MUGA scan will be performed at Screening to determine eligibility. Additional scans will be performed only if clinically indicated.
  - **NOTE**: the same method of cardiac evaluation must be used consistently for any follow-up scans.

- ECGs (refer to Appendix 3 for the ECG parameters required). Duplicate ECGs are required at screening only (prior to leukapheresis) as long as the subject remains asymptomatic and remains within parameters.
- Cardiac troponin I or cardiac troponin T will be assessed throughout the study. Site may select either test as long as the same assay is used consistently for the subject.
- A chest x-ray will be performed at Baseline. Additional x-rays should be performed if clinically indicated.
- Pulmonary function tests will be performed at Screening to determine eligibility (refer to Section 4.2.2 for the parameters required)
- For subjects with known cardiac or pericardial tumor involvement at baseline, inpatient telemetry monitoring should be carried out for a minimum of seven days post MAGE-A10 infusion.

Refer to Schedule of Procedures (Table 6) for information regarding the frequency of these assessments.

7.4.7. Tumor Response Assessments

Tumor assessments for response and PD will be evaluated at Baseline (within 7 days of lymphodepleting chemotherapy), Week 4, Week 8, Week 12, Week 24, every 3 months until Year 2 and then every 6 months thereafter until PD, according to RECIST v1.1 (refer to Appendix 4) (Eisenhauer, 2009). The Week 4 scan be obtained Day 28±3days. Subsequent scans are to be completed within the visit window permitted in the protocol with the exception of confirmatory scans which should not be performed earlier than 4 weeks (on or after 28 days) after the criteria for response was first met.

Imaging scans of the chest, abdomen and pelvis should be performed at Baseline and all subsequent visits. 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);
- Magnetic resonance imaging (MRI) of the abdomen/pelvis acquired before and after gadolinium contrast agent administration and a non-contrast enhanced CT of the chest, if a subject is contraindicated for contrast enhanced CT;
- MRI of the extremities per site standard of care, if clinically indicated;
- Digital photographs of skin lesions including a ruler for estimating the size of the lesion.

An MRI or the brain with contrast should be obtained at Screening and at Baseline (within 1 month prior to lymphodepletion). CT with IV contrast may be used only for subjects with contraindications to MRI brain. If CNS metastases are documented at Screening or Baseline, 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 or Baseline, then dedicated CNS CT/MRI scans should be performed as clinically indicated.

Bone scans may be performed if bone metastases are suspected and should be repeated to confirm a complete response or if progression of existing bone lesions and/or the development of new bone lesions is clinically suspected.

The same imaging modality and image-acquisition protocol (including the use of IV contracts) should be used consistently across all time points for individual subjects to allow uniform comparisons of lesions.

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

To allow time for the immune response to become apparent and for potential transient inflammatory reaction of the disease to the treatment ('tumor flare'), response should not be assessed before 4 weeks ±3days post infusion of MAGE-A10^{c796}T, unless there is unequivocal clinical evidence of deterioration. Response or progression should be confirmed by repeat imaging scan performed not earlier than 4 weeks after the criteria for response or progression was first met. If there is unequivocal evidence of PD and/or the need for an alternate anti-cancer treatment a confirmatory scan is not required. Determinations of PD will be based upon RECISTv1.1.

In patients with symptomatic deterioration of disease, every effort should be made to document objective progression by evaluation of target and non-target lesions. Patients with a global deterioration of health status without objective evidence of disease progression at that time should be reported as clinical progression.

For new lesions, information on whether the lesion is measurable or non-measurable will be recorded in the eCRF. The measurements of measurable lesions will also be recorded.

CT/MRI scans will be collected and stored at a central imaging vendor for a possible independent review at the discretion of the Sponsor. A Site Imaging Manual will be provided to sites to describe the imaging acquisition and standardized procedure for the transfer of image data to the central imaging vendor. The Site Imaging Manual will also describe the procedures for CT/MRI data handling after the images have been received by the central vendor from the sites.

7.4.8. Long-Term Follow-up

All subjects will be followed for 15 years from the time of their last T cell infusion for observation of delayed AEs in accordance with FDA and EMA requirements for gene therapy clinical trials (FDA, 2006a; FDA, 2010; EMEA, 2009). If a subject receives a second T cell infusion, the 15 year clock restarts with the second infusion.

Subjects will then be seen in the clinic for evaluation according to Schedule of Procedures (Table 6) until the end of the Interventional Phase (Section 4.5, Section 4.6.1). Thereafter, subjects will enter the LTFU Phase and will undergo assessments/procedures according to the LTFU Schedule of Procedures (Table 7).

Subjects will continue to be followed for overall survival during the LTFU Phase.

Reporting criteria for AEs related to gene therapy during LTFU are described in Section 9.4.

7.4.9. 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'.

7.5. Correlative Studies and Research Assessments

Correlative studies and research assays will be performed during the trial with the aim of monitoring the biological parameters that influence treatment outcome, such as [redacted] persistence of the engineered infused cells, as well as evaluation of candidate biomarkers of immune response, antitumor activity and resistance to therapy. Data from such studies will be correlated to clinical outcome. These studies will be performed on blood, tumor biopsies [redacted] collected according to the Schedule of Procedures (Table 6).

[redacted]

[redacted]

7.5.1. Cytokine and Soluble Factors Analysis

Serum will be collected at Baseline, pre-T-cell infusion, and at each specified visit post-infusion up to 12 weeks, then after Week 24 at every 3 months up to 2 years to allow for measurement of cytokines in the blood. Serum will also be collected from subjects with suspected CRS, with samples being taken approximately every other day until symptoms are improving or an alternative diagnosis is confirmed (refer to Section 8.5). Details regarding serum collection are provided in the SPM or Laboratory manual.

[redacted]

7.5.2. Tumor Biopsies

The efficacy of cancer immunotherapy is conditioned by the infiltration of tumors by activated tumor-specific T cells. The activity of these T cells will in turn be affected by the presence in the tumor of an immunosuppressive environment [redacted]. Therefore, the direct evaluation of the "immune landscape" inside the tumor is of great value for understanding and optimizing cancer immunotherapy. For this reason, core needle biopsies are requested at Screening (through Screening Protocol, ADP-0000-001), Baseline (to evaluate the immune status of the tumor before T cell infusion), Week 3 (+5 weeks, at the expected time of an active anti-tumor response by infused T cells), and after disease progression is confirmed, with the exception of subjects for whom there is no safely accessible tumor tissue.

Archival tissue may be used for the screening biopsy, although fresh tissue is preferred. If a fresh biopsy was taken for MAGE-A10 confirmation screening in the Screening Protocol (ADP-0000-001), and there is sufficient tumor sample left remaining, this sample may be used as the baseline sample for these correlative science studies. Baseline biopsy material (either obtained from the Screening Protocol or a new Baseline biopsy) should be collected within two months of the T cell infusion, with preference for a biopsy to be taken closer to the time of infusion. Tumor tissue should either be taken from non-target lesions or from target lesions where sampling can be done without significantly impacting lesion measurement. [redacted]

Additional details regarding tumor biopsy collection are provided in the SPM or Laboratory Manual.

[redacted]

[redacted]

7.5.3. MAGE-A10^{c796} TCR^{+} Cell Persistence:

The primary research assays for the trial involve monitoring for the persistence of infused engineered cells in the subjects and for correlation of this with potential therapeutic effect. Persistence is also monitored as a long-term safety measure (refer to Section 10.2). [redacted]

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

In accordance with FDA and EMA guidance (FDA, 2006a; EMEA, 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. To ensure compliance, guidelines for performing an autopsy are provided in the SPM.

8. 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 during the dose escalation phase of the study and may be discharged if medically stable at the discretion of the Investigator. Staff treating trial subjects should be experienced in acute post-transplant care and the management of associated toxicities (e.g. cytopenias, CRS, autologous GVHD, encephalopathy syndrome).

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.

8.1. T Cell Infusion Symptom Management

Mild transient symptoms have been observed following 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 that develop fever or chills have a full investigation for infection, including a blood culture.
- Nausea and vomiting may be treated with a non-steroidal anti-emetic of choice.
- Hypotension will initially be managed by intravenous 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.

8.2. 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.

8.2.1. 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 (1500mg daily with food) or **IV** pentamidine (300mg every four weeks) are also acceptable in cases of sulfonamide allergy or sulfa intolerance. Treatment should follow Institutional standards for autologous bone marrow transplants.

8.2.2. Herpes simplex and Varicella zoster

All subjects should receive prophylaxis with acyclovir (800mg twice daily) or valacyclovir (500mg twice daily) for one year, or in accordance with institutional guidelines.

8.2.3. Cytomegalovirus

All subjects will be screened for cytomegalovirus (CMV) IgG seropositivity at study entry. If CMV viremia is detected at Baseline, treatment should be initiated with evidence of viral clearance prior to lymphodepleting chemotherapy. All CMV IgG seropositive subjects will continue to be monitored as shown in Table 6 for CMV viremia by CMV DNA PCR until 60 days post infusion of MAGE-A10^{c796}T cell therapy. 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 8.7.

8.2.4. Hepatitis B Prophylaxis

Subjects will be screened for hepatitis B (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 chemotherapy and continued for 6 months. Acceptable regimens include lamivudine (300mg daily), entecavir (0.5mg daily), or tenofovir (300mg daily).

8.2.5. Syphilis

Subjects will be screened for syphilis at study entry. 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 lymphodepleting chemotherapy.

8.2.6. Other Anti-Microbial Prophylaxis

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

8.3. Hematologic and Blood Product Support

Blood product support should be provided to maintain platelets >10 x10^9/L, hemoglobin >8.0 g/dL (or in accordance with institutional practice) and as clinically indicated. Refer to AABB Guideline on platelet transfusion (Kaufman, 2015).

8.3.1. Irradiated Blood Product

Bone marrow suppression can be a consequence of transfusion associated GVHD. To minimize the possibility of transfusion associated GVHD, all blood products transfused within 4 weeks prior to leukapheresis, within 4 weeks prior to initiation of lymphodepleting chemotherapy and following lymphodepleting chemotherapy until at least 6 months following IP infusion or until lymphocyte count returns to ≥1.0 x10^9/L (whichever is longer) must be irradiated. In addition, if a subject requires systemic steroids or immunosuppression for the treatment of toxicity, irradiated blood products must be given until recovery of immune function.

8.3.2. CMV Screened Blood Products

All subjects will be screened for CMV seropositivity. 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 the LTFU Phase.

8.4. 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 Investigator should be contacted and every attempt should be made to biopsy the affected organ to clarify whether the symptoms are related to the MAGE-A10^{796}T cell 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.

8.5. Management of Cytokine Release Syndrome

Cytokine release syndrome is a potentially life-threatening toxicity that has been observed following administration of antibodies and ACT for cancer. It is defined clinically by symptoms, many of which mimic infection, including pyrexia, nausea, diarrhea, headache, fatigue, tachycardia, hypotension, transaminitis, rash, and dyspnea. 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 causes a 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).

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 and C-reactive protein levels as described in Section 7.5.1 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, and/or Grade 2 organ toxicity)	• 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. • Consider administering anti-IL-6 therapy[3] (tocilizumab 8 mg/kg* 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]
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). *The maximum dose for tocilizumab is 800 mg per dose. Corticosteroids can be used for subjects 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) for tocilizumab recommends a dose of 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 8.8 below for subjects experiencing encephalopathy concurrent with CRS.

Subjects unresponsive to anti-IL-6 therapy may require treatment with steroids. Lee et al., 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 anti-tumor effects of the ACT. However, in subjects with Grade 3 or 4 CRS associated with neurologic dysfunction without significant hemodynamic instability (see Section 8.8) 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 note that product labels are subject to change and the most current version of the product label for tocilizumab should be referenced if there are any questions.

8.6. Management of Graft-versus-Host Disease (GVHD)

Autologous GVHD has been described in association with adoptive transfer of ex-vivo expanded/co-stimulated autologous T-cells (Rapoport, 2009), as well as infusion of T-cells with engineered specificity for NY-ESO-1 and LAGE-1a (Garfall, 2013), following high-dose chemotherapy and autologous stem cell transplant (ASCT) in subjects with multiple myeloma. There is the potential for subjects who receive lymphodepleting therapy followed by engineered autologous T-cell infusion to experience GVHD and/or autoimmune GVHD-like symptomatology. Autologous GVHD is typically milder than classic (allogeneic) GVHD (Kline, 2008), and is usually manageable with treatment. However, severe cases (including fatalities) have been reported (Fidler, 2012). There are no published guidelines for the management of autologous GVHD. However, lessons can be drawn from published cases

reports and guidelines for the diagnosis and management of acute GVHD following allogeneic transplant (Dignan, 2012).

8.6.1. Diagnosis of GVHD

The diagnosis of GVHD is predominantly based on clinical findings and is often one of exclusion (Table 9). Many of these symptoms can also occur in the setting of the preparative regimen, high dose cyclophosphamide as well as with CRS. Any of these conditions including GVHD can be associated with fever. The skin is the most commonly involved organ, followed by the gastrointestinal (GI) tract and liver. A constellation of symptoms involving these organ systems may be helpful in establishing the diagnosis of GVHD. Diarrhea, rash, fever, and pancytopenia are common toxicities in the NY-ESO-1^{c259}T program where we have the most clinical experience. Mild (Grade 1 or 2) transient transaminitis without cholestasis has been observed.

Table 9: Overview of Clinical Findings/Symptoms of GVHD

Organ	Findings/Symptoms	Differential Diagnosis	Histopathology
Skin	Maculopapular rash involving the neck and shoulders as well as the palms and soles that spreads to include the rest of the body.	Drug reactions, viral exanthems, CRS, and effects of chemotherapy or radiation	Apoptosis at base of epidermal rete pegs, dyskeratosis, exocytosis of lymphocytes, satellite lymphocytes adjacent to dyskeratotic epidermal keratinocytes and perivascular lymphocytic infiltration in the dermis.
GI	Secretory diarrhea is most common but nausea, vomiting, anorexia, weight loss and abdominal pain can also occur. Diarrhea can be copious. Bleeding may result from mucosal ulceration and ileus may ensue.	Side effects of chemotherapy or other drugs and infection of the GI tract	Patchy ulcerations, apoptotic bodies at crypt bases, crypt ulceration and flattening of surface epithelium
Liver	Cholestatic pattern of liver injury including elevated conjugated bilirubin, alkaline phosphatase and GGTP. Subjects may present with jaundice, with pruritis in more severe cases.	Veno-occlusive disease of the liver, viral infections, drug toxicity and sepsis.	Endothelialitis, lymphocytic infiltration of the portal areas, pericholangitis and bile-duct destruction.

NOTE: Bone marrow suppression and related cytopenias have been described in the setting of acute GVHD. Management of this complication is challenging, with no clearly established guidelines regarding immunosuppression. Treatment may be largely supportive, including transfusions and treatment of infections.

Management should include consultation with a physician with expertise in the management of subjects following bone marrow transplant.

Bone marrow suppression is also a feature of transfusion-related GVHD. To minimize the possibility of transfusion-related GVHD, refer to Section 8.3.1 for guidance on irradiated blood products.

8.6.2. Grading of GVHD

Grading of acute GVHD is based on the stage of dermal, gastrointestinal, and hepatic involvement as described in Table 10 Careful measurement of stool volume and assessment of percentage of body area covered by rash are important for proper grading and treatment.

Table 10: Staging of Dermal, Gastrointestinal and Hepatic Involvement with Acute GVHD

Stage	Skin	Gut	Liver
1	Maculopapular rash <25% of body area	Diarrhea >500 ml/day	Bilirubin 2-3 mg/dl
2	Maculopapular rash 25%-50% of body area	Diarrhea >1,000 ml/day	Bilirubin 3-6 mg/dl
3	Generalized erythroderma	Diarrhea>1,500 ml/day	Bilirubin 6-15 mg/dl
4	Desquamation and bullae	Diarrhea>2,000 ml/day or pain or ileus	Bilirubin >15 mg/dl

With the addition of assessment of functional impairment, grading can be determined using Table 11 (Glucksberg, 1974).

Table 11: Grading of Acute GVHD

Grade	Skin[1]	Gut[1]	Liver[1]	Functional status[2]
I	1-2	0	0	0
II	1-3	1	1	1
III	2-3	2-3	2-3	2
IV	1-4	2-4	2-4	3

[1] Staging is described above
[2] Mild, moderate, or severe decrease in performance status

8.6.3. Management of GVHD

Although the diagnosis of GVHD is predominantly based on clinical grounds, biopsy of affected organs can be helpful in excluding other causes and supporting the diagnosis of GVHD with consistent histopathologic findings. However, awaiting biopsy results should not delay the institution of appropriate therapy.

If GVHD is suspected:

- A physician with expertise in the management of subjects following bone marrow transplant should be consulted
- Consider biopsy of the affected organ(s)

Corticosteroids have been used as the standard first-line treatment for GVHD for several decades. Their effect is likely to be due to lympholytic effects and anti-inflammatory properties. In general, intestinal and liver GVHD require more prolonged steroid therapy than skin disease although response times vary.

Diarrhea should be managed with volume replacement, dietary restriction, and anti-diarrheal agents including the consideration of somatostatin for secretory diarrhea. Agents that slow motility should be used cautiously, ensuring that there is no evidence of ileus or toxic megacolon, and infectious causes of diarrhea should be excluded.

General guidelines for first-line treatment based on grade are provided in Table 12, and should be considered in conjunction with input from the consulting physician with bone marrow transplant expertise.

Table 12: Management Guidelines for GVHD

Grade	Management Strategy
I	Subjects with Grade I disease are not likely to require systemic treatment. Cutaneous GVHD may respond to topical steroid creams. Antihistamines may be helpful in subjects with pruritis. Subjects should be reviewed frequently for other organ manifestations of GVHD.
II	Treat skin symptoms with topical steroids. For GI symptoms - optimize anti-diarrheal regimen, dietary restrictions, volume replacement and consider initiation of non-absorbable steroids. For refractory or progressive symptoms consider systemic steroids as outlined below.
III	For more severe or progressive symptoms consider systemic corticosteroids (e.g., methylprednisolone one (1) mg/kg per day[1])
IV	Methylprednisolone two (2) mg/kg per day[1]

[1] The use of 'nonabsorbable' steroids (Budesonide and beclomethasone) can be considered for acute intestinal GVHD in order to reduce the dose of systemic steroids

If high dose corticosteroids are required, treatment should generally be continued for at least 5 days followed by tapering doses over several weeks. A physician with expertise in infectious diseases in immunocompromised hosts should be consulted, and prophylactic antimicrobials should be considered.

Second-line treatment can be considered for subjects who have failed to respond for 5 days or have progressive symptoms after 3 days. There is no clear second-line agent that is preferred for steroid refractory GVHD. General guidelines for second-line treatment based on grade are provided below, and should be considered in conjunction with input from the consulting physician with bone marrow transplant expertise.

For steroid refractory skin rash, topical tacrolimus may also be useful.

Most of the allogeneic transplant subjects are concurrently receiving calcineurin inhibitors in part as prophylaxis against GVHD. Therefore, for Grade II-IV disease refractory to high dose steroids, the addition of a calcineurin inhibitor can be considered.

Otherwise, there are several additional second-line treatment options for which there is currently limited and/or evolving supporting data. Treating physicians can refer to the Haemato-oncology Task Force of the British Committee for Standards in Haematology and the British Society for Blood and Marrow Transplantation guideline for diagnosis and management of acute graft-versus-host disease (Dignan, 2012).

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

Pancytopenia with bone marrow failure / aplastic anemia has been reported after initial bone marrow recovery from high-dose chemotherapy followed by infusion of NY-ESO-1^{c259}T-cells. 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. 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: ANC <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:

- Consult a physician with expertise in the management of aplastic anemia
- Increase the frequency of CBCs as clinically indicated.
- Exclude other alternative etiologies such as other drugs, viral causes, etc.
- 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 SPM or Laboratory Manual and refer to Section 7.5.
- A matched peripheral blood sample should be collected in parallel with the bone marrow sample and provided to the Sponsor. Refer to Section 7.5.
- Initiate treatment with G-CSF
- Consult an Infectious Diseases expert
- Once alternative etiologies have been excluded, strongly consider immunosuppression (e.g. methylprednisolone 2mg/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/ID consultant(s). If high dose corticosteroids are initiated, continue for a minimum of 5 days and taper gradually with advice from expert consultants.

Refer to Section 8.6 regarding bone marrow suppression as a feature of GVHD.

8.8. Management of Encephalopathy syndrome

Encephalopathy has been described in association with chimeric antigen receptor (CAR) T therapy, and termed (CAR) T cell related encephalopathy syndrome, or CRES Neelapu S. et al. (2018) Chimeric antigen receptor T‐cell therapy-assessment and management of toxicities. Nature Reviews-Clinical Oncology 15: 47-62.). 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 1–2, see Table 14), and is generally reversible with anti-IL-6 therapy. CRES presenting as delayed neurotoxicity with seizures or episodes of confusion can occur three or four weeks after CART‐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 encephalopathy syndrome in relation to T cell therapy.

8.8.1. Grading of ES

Neelapu S. et al. (2018) Chimeric antigen receptor T‐cell therapy-assessment and management of toxicities. Nature Reviews-Clinical Oncology 15: 47-62.) have developed a new grading system for ES which incorporates the CARTOX 10‐point neurological assessment (CARTOX‐10) tool, see Table 13. Points are assigned for each of the tasks in Table 13which 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.

Table 13: 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 (one point for each)
Name three objects, for example point to: clock, pen, button	Total of 3 points (one point for each)
Write a standard sentence, e.g. '*our national bird is the bald eagle*'	1 point
Count backwards from 100 in tens	1 point

The CARTOX-10 score is used in grading of ES as presented in Table 14.

Table 14: Grading of Encephalopathy Syndrome (ES)*

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
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 13for CARTOX-10.
[2] Papilledema grading is performed according to the modified Frisén scale.
* Based on Neelapu S. et al. (2018) Chimeric antigen receptor T-cell therapy-assessment and management of toxicities. Nature Reviews-Clinical Oncology 15: 47-62.).

8.8.2. Monitoring for ES

Brain MRI (or CT Scan if MRI not feasible) is recommended at the time of screening and it is required at baseline for all subjects.

CARTOX-10 should be measured on the day of MAGE-A10^{c796}T infusion prior to receiving treatment and then at least through Day 8 according to the schedule of procedures. Subjects with known brain metastases should be monitored at least twice per day for the first 5 days following MAGE-A10^{c796}T infusion. If a subject is found to have ES, the CARTOX-10 should be used at least twice per day until resolution or stable. It can also be used at later visits if indicated.

8.8.3. Management of ES

The recommended management of ES should be based on toxicity grade. Table 15 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.

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 8.5 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 as below for thorough neurological evaluation, and recommendations for further testing such as EEG and neuroimaging as indicated.

Table 15: Management of encephalopathy syndrome (ES)

Grade	Treatment
1	For all subjects: • Vigilant supportive care; aspiration precautions; intravenous (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 fundoscopic 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* IV or siltuximab 11 mg/kg IV, if Grade 1 persists beyond 24 hours, or worsening and associated with concurrent cytokine-release syndrome (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
4	Supportive care and neurological work‑up as outlined 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

* Maximum amount of tocilizumab per dose is 800mg

8.9. 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, and Section 6.1 for details of prohibited medications.

8.9.1. Management of Neutropenia

The pre-conditioning chemotherapy is intended to cause lymphodepletion. However, neutropenia is also common. Prophylactic use of G-CSF should be used in all subjects. G-CSF should be given on Day -3 until resolution of neutropenia (reaching an ANC of at least 2 $\times$ 10^9/L to 3 $\times$ 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 should be given as one dose on Day -3.

In addition, G-CSF should be used for management of neutropenia according to ASCO guidelines (Smith, 2015) or as per institutional practice.

9. RECORDING ADVERSE EVENTS

Timely, accurate and complete reporting and analysis of safety information from clinical studies are crucial for the protection of subjects and is mandated by regulatory agencies worldwide. The Sponsor has established standard operating procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of all safety information; all clinical studies conducted by the Sponsor or its affiliates will be conducted in accordance with those procedures. The Investigator and their designees are responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE. Individual AEs should be evaluated by the Investigator and should be reported to the Sponsor as appropriate. This includes the evaluation of its intensity, the causality between the investigational medicinal product and/or concomitant therapy and the AE and seriousness.

The Sponsor has to keep detailed records of all AEs reported by the Investigator(s) and to perform an evaluation with respect to causality, seriousness, and expectedness.

9.1. Time Period for Collecting AE and SAE Information

AEs and SAEs will be collected at the time points specified in the Schedule of Procedures (Table 6) and as described herein:

- From the date of signing informed consent until the day before lymphodepleting chemotherapy starts, only SAEs related to study design/procedures (protocol mandated procedures, invasive tests, or change in existing therapy) and AEs leading to withdrawal from the study will be collected.
- All AEs and SAEs will be collected from the start of lymphodepleting chemotherapy until the subject has disease progression following their last T cell product infusion. Refer to Section 9.4 for details on emerging clinical conditions that must be reported post-infusion.

– **NOTE**: If the subject has not progressed 12 months after infusion, then only those emerging clinical conditions defined in Section 9.4 will be collected. Collection of all AEs/SAEs is no longer required.

9.2. Definition of Adverse Event

In accordance with the International Conference of Harmonization (ICH), an AE is any untoward medical occurrence in a subject or clinical investigation subject who receives a pharmaceutical product, regardless of causality. An AE is therefore any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product. Pre-existing conditions which worsen during the study are to be reported as AEs. For guidance on reporting laboratory test abnormalities as AEs, refer to Section 9.9.

Adverse events or abnormal laboratory findings should be recorded in the eCRF using a diagnosis or possible diagnosis, and rated for intensity, causality and seriousness. In the absence of a diagnosis, individual symptoms or findings may be recorded and the eCRF updated to reflect a final diagnosis once additional information becomes available. If photographs are requested by the Sponsor (e.g. a rash AE), the subject will sign a Medical Photograph Release prior to any photographs being taken.

All AEs should be followed until:

- Resolved or improved to baseline.
- Investigator confirms no further improvement can be expected.
- Death

On completion of the subject from the Interventional Phase of the study, or withdrawal from the study, serious or severe AEs will be followed until one of the above criteria is met. SAEs related to MAGE-A10^{c796}T will continue to be recorded and monitored into long-term follow-up (refer to Section 9.4).

9.2.1. Assessment of Intensity

AEs will be graded according to the NCI CTCAE v4.0. The Investigator will assess intensity of all AEs using this five point scale (Grade 1-5) and record on the eCRF.

AEs not specifically listed in the CTCAE should be graded according to Table 16:

Table 16: Grading of AEs Not Specified in CTCAE v4.0

CTCAE Grade	Equivalent to	Definition
Grade 1	Mild	Discomfort noticed but no disruption of normal daily activity
Grade 2	Moderate	Discomfort sufficient to reduce or affect daily activity; minimal medical intervention is indicated.
Grade 3	Severe	Incapacitating with inability to work or perform normal daily activity; treatment or medical intervention is indicated in order to improve the overall well-being or symptoms; delaying the onset of treatment is not putting the survival of the subject at direct risk.
Grade 4	Life-threatening/ disabling	An immediate threat to life that requires urgent medical intervention
Grade 5	Death	AE resulting in death.

9.2.2. Assessment of Causality

The Investigator will assess the causal relationship between the AE and MAGE-A10^{c796}T according to his/her best clinical judgement. An assessment of possibly/probably/definitely related is meant to convey there is evidence of a causal relationship, not that a relationship cannot be ruled out. The Investigator should consider alternative causes such as natural history of the underlying disease, lymphodepleting chemotherapy, concomitant medications and other risk factors when making an assessment. The following scale will be used as guidance:

- **Not related** – The subject did not receive the investigational product; the temporal sequence of the AE onset relative to administration of the investigational product is not reasonable; or there is another obvious cause of the AE.
- **Possibly related** – There is evidence of exposure to the investigational product; the temporal sequence of the AE onset relative to T cell infusion is plausible; or the AE could have been due to another equally likely cause.
- **Probably related** – There is evidence of exposure to the investigational product; the temporal sequence of the AE onset relative to T cell infusion is plausible; the AE shows a pattern consistent with previous knowledge of the investigational product; or the AE is more likely explained by the investigational product than any other cause.
- **Definitely related** – There is evidence of exposure to the investigational product; the temporal sequence of the AE onset relative to T cell infusion is plausible; the AE shows a pattern consistent with previous knowledge of the investigational product, or the AE is most likely explained by the investigational product and any other cause is improbable.

The Investigator may change his/her opinion of causality if additional information is received, and amend the AE eCRF accordingly. The Investigator causality assessment is one of the criteria Adaptimmune use to determine regulatory reporting requirements for an SAE.

9.3. Reporting Serious Adverse Events (SAEs)

An SAE is any AE that:

- Results in death (**NOTE:** death is the outcome, not the event).
- Is life-threatening (**NOTE:** the term "life-threatening" refers to an event in which the subject was at immediate risk of death at the time of the event; it does not refer to an event which could hypothetically have caused a death had it been more severe).
- Requires hospitalization or prolongation of existing hospitalization.
- Results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- Is a congenital anomaly/birth defect.
- Is medically significant or requires intervention to prevent one of the outcomes listed above.

Medical and scientific judgment should be exercised in deciding if an AE is of significant enough medical importance to be classified as serious outside the above definitions. Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-subject hospitalization or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

Additional protocol-defined criteria

- Any Grade ≥3 CRS or GVHD must be reported as an SAE and is subject to expedited reporting (Section 9.6)

The study will comply with all local regulatory requirements and adhere to the full requirements of the ICH Guideline for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting, Topic E2.

An SAE must be reported to Adaptimmune by completing the paper SAE worksheet (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

Details pertaining to the SAE must be completed by the Investigator with as much available information about the event. The minimum reporting criteria for an SAE include:

- Identifiable subject (Subject ID)
- Suspect investigational product
- Identifiable reporting source (PI acknowledgement of the report and his/her signature is required)
- Event that is identified as serious (SAE term)
- Toxicity grade
- Relationship to investigational product

The Investigator will assess the causal relationship between the SAE and investigational product according to his/her best clinical judgement. The Investigator will also assess the causal relationship between the SAE and the lymphodepleting chemotherapy.

Please refer to the SPM for the SAE Worksheet.

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

Due to the nature of the treatment, subjects are required to be followed for up to 15 years after treatment with genetically modified T cells according to FDA and EMA guidance (FDA, 2006a; FDA, 2010; EMEA, 2009).

Subjects will be followed according to the schedule outlined in Table 6 and will continue to be monitored in the LTFU phase per Table 7. During the LTFU Phase, subjects will only be monitored for potential gene therapy-related delayed adverse events as defined below. Emergence of any of the following new clinical conditions reported or observed and the action taken will be reported to the Sponsor as an AE or an SAE if the LTFU event meets the serious criteria defined in Section 9.4:

- 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 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 related to gene modified cell therapy

These are the only adverse events that will be collected in the LTFU Phase of the study.

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 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 reports of the Investigational New Drug (IND) 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 .

9.5. Progression of Underlying Malignancy

Progression of underlying malignancy and related symptoms are not 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 symptom cannot be determined as exclusively due to the 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.

9.6. Regulatory Reporting Requirements for SAEs

The Sponsor has legal obligations for expedited reporting of certain events to Regulatory Authorities, IRBs (Institutional Review Board)/Independent Ethics Committees (IEC) and other study participants. Adaptimmune will comply with country specific regulatory requirements relating to safety reporting to the Regulatory Authorities, IRBs/IECs and Investigators.

Investigator safety reports are prepared for SUSARs according to local regulatory requirements and Adaptimmune policy. These safety reports are forwarded to Investigators as necessary in the form of Investigator Safety Letters.

An Investigator who receives an Investigator Safety Letter describing a SAE(s) or other specific safety information (e.g. summary or listing of SAEs) from Adaptimmune will file it with the Investigator Brochure and notify their IRB/IEC if appropriate, in accordance with 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 which are reported to him by the relevant Investigator(s).

9.7. Pregnancy

There is no pre-clinical or clinical trial data of MAGE-A10^{c796}T 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 lymphodepleting chemotherapy and for at least 12 months after receiving the investigational product or for four months after there is no evidence of persistence/gene modified cells in the subject's blood, whichever is longer.

Pregnancy (or pregnancy of a male subject's partner) is not considered an AE/SAE unless there is reason to believe that the pregnancy may be the result of failure of the contraceptive being used due to interaction with the investigational product. However, the Investigator shall report all pregnancies immediately to the Sponsor. Women who become pregnant and remain pregnant during the study will be discontinued from the Interventional Phase as exposure to radiation from imaging studies would be contraindicated in this setting. The subject would enter the LTFU Phase. The outcome of the pregnancy must also be reported to the Sponsor. The contraception guidelines in the inclusion criteria of the parent protocol should continue to be followed during LTFU.

9.8. Pre-existing Condition

A pre-existing condition is one that is present at the start of the study during Screening. A pre-existing condition should be recorded as an AE if the frequency, intensity, or the character of the condition worsens during the Interventional Phase.

9.9. Laboratory Test Abnormalities as Adverse Events

Out of range laboratory test results meeting the following criteria, should be reported as AEs.

- Any CTCAE laboratory value Grade ≥3 should be recorded as an AE. Grade 1 and 2 laboratory abnormalities do not require reporting unless the Investigator considers the event as clinically significant.
- Any Grade 4 CTCAE laboratory value based solely on numerical criteria (e.g. white blood cells decreased) should be reviewed to determine whether it should be reported as a SAE.

10. SAFETY MONITORING

10.1. 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). Updated γ retroviral packaging systems have not been associated with RCR. However, in a study with Rhesus monkeys, three out of 10 animal died of lymphomas at around 6 months after transplantation of vector transduced bone marrow cells contaminated with replication-competent virus (Donahue, 1992). Therefore, RCR/L must continue to be rigorously evaluated in vector and cell lots, and in subjects post infusion with any product involving a retrovirus (FDA, 2006b; FDA, 2010; EMEA, 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 between homologous or non-homologous recombination between the transfer vector and packaging elements, or endogenous retroviral elements (Garrett, 2000; Chong, 1998). 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 a RCL by recombination with an endogenous virus (i.e., HIV) in the subject following infusion of the vector 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 virus, or could increase the replication rate or pathogenicity of the subject's 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.

Regulatory Agencies and the gene therapy community have previously discussed measures to be taken should an RCL be confirmed in a subject (FDA, 2006a; FDA, 2006b; EMEA, 2009). However, because the probability and characteristics of an RCL are unknown, no concrete plans have been put in place. As of the writing of this protocol, it is agreed that the subject must be isolated and no additional subjects treated with MAGE-A10^{c796}T cells until an action plan is agreed upon as outlined in Section 10.1.2.

The following approaches have been discussed for subject management:

- Provide targeted antiretroviral therapies based on genotyping of the RCL.
- Intensive follow up of subject in consultation with FDA, and other Regulatory Authorities, NIH, gene therapy experts, study Investigators, and HIV physicians.

10.1.1. Testing for RCL in Clinical Studies

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 Vesicular Stomatitis Virus G protein (VSV-G) that is necessary for the assembly of pseudotyped infectious lentiviral particles but absent from the vector's backbone. RCL testing and monitoring will take place on

- The cell product, whereby RCL testing will be performed by or under the direction of the manufacturing facility responsible for vector manufacturing and release of the vector.
- Subject PBMC samples which will be collected prior to infusion of transduced T cells 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 these tests are negative at all time points during the first year, PBMC samples will be collected annually until Year 15 and archived at Adaptimmune's centralized biorepository.

10.1.2. Safety Monitoring Results

If a positive VSV-G DNA signal is obtained, the Investigator will be informed and the subject 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 Adaptimmune's Safety Review Team and 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, at which time the subject samples will be collected and archived annually until 15 years post-infusion
- If the second test is positive, infusions for all subjects receiving 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 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 is positive, all MAGE-A10^{c796}T cell infusions 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 until such time as a plan is completed, reviewed and agreed upon.

10.2. Persistence Testing and Monitoring for Insertional Oncogenesis

Monitoring for insertional oncogenesis follows the recommendations set forth in the FDA and EMA guidance (EMEA, 2009; FDA, 2006a; FDA, 2006b). 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 (SCID-X1) 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 (Hacein-Bey-Abina, 2003; Hacein-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).

10.2.1. Testing for Persistence of Gene Marked Cells in Clinical Studies

Peripheral blood mononuclear cells samples will be collected and used as the "surrogate sample" for monitoring persistence of gene modified cells in subjects prior to infusion of transduced T cells (Baseline) and at 6, and 12 months post-infusion, then every 6 months until 5 years post-infusion and annually from Year 6 to 15 post infusion in accordance with the FDA and EMA guidance (EMEA, 2009; FDA, 2006b). The samples will be tested using a PCR-based method to detect the presence of the Packaging signal (Psi) sequence, 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% of PBMCs test positive for vector sequences, then the subject's PBMCs will be evaluated for integration site analysis (refer to Section 10.2.2). If no gene modified cells are detected for three consecutive assessments post-infusion, and the subject is ≥5 years post-infusion (for example, negative persistence assessments at year 4, 4.5 and 5), then no further monitoring of PBMCs is required and collection of samples for persistence may be discontinued. Hematology and chemistry may also be discontinued. NOTE: Samples for RCL must continue to be collected and archived annually until 15 years post-infusion. Subject will continue to be followed by the Investigator for up to 15 years post-infusion. The Investigator will be the primary physician responsible for continued follow up of the subject

for the duration of LTFU, whenever possible. If contact with the Investigator becomes no longer feasible, follow up can be transitioned to a local physician, preferably an oncologist.

10.2.2. Testing for Insertional Oncogenesis

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 call population (either monoclonality or oligoclonality), the persistence assessment will be repeated within 3 months on a new sample. If the repeated analysis demonstrates: 1) persistent monoclonality, 2) evidence of insertional oncogenesis or 3) clonal expansion (an increase in percent predominance of a clone), there will be a review by Adaptimmune's Safety Review Team and 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 will continue as scheduled.

10.3. Safety Review Committee

A SRC will be implemented in this study and will consist of one external physician with expertise in oncology and adoptive cell therapies who is unaffiliated to the Sponsor's studies, and up to two more external physician investigators; 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. Recommendations on study modification, including cohort expansion or escalation, and decisions around halting the study and/or enrollment will be made by the SRC. A SRC charter, defining roles and accountabilities and the process for safety review, will be available.

11. STATISTICAL AND DATA ANALYSIS

The objectives and endpoints for this study are described in Section 2. Section 11 focuses on key aspects for the analysis and reporting of the primary and secondary efficacy and safety endpoints. Details for the analysis of all endpoints, including subgroups, sensitivity analyses and missing value imputations, such as censoring, where applicable, will be provided in the Statistical Analysis Plan (SAP). The safety and efficacy data for subjects from the UK may be summarized separately.

11.1. Study Populations

Intent-to-Treat (ITT) population: all subjects who have met eligibility criteria. [redacted]

Modified ITT (mITT) population: all subjects in the ITT population who receive at least one MAGE-A10^{c796}T cell infusion.

If the mITT and ITT populations are identical, only analyses associated to the ITT population will be reported.

Detailed criteria for inclusion in these populations will be prospectively specified in the SAP.

Further exploratory analysis populations may be defined according to the correlative studies.

11.2. Sample Size Calculations

The sample size of up to 10 subjects treated at the target dose is based on clinical judgment. This is a small Phase I study to describe the safety and tolerability where efficacy endpoints are secondary and will be summarized using estimation methods such [redacted] The study is not powered to conduct statistical hypothesis testing.

11.3. Interim Analyses

No formal statistical interim analyses for efficacy or futility are planned for this study.

11.4. Statistical Methods for Safety Endpoints

Safety endpoints will be summarized by time periods, described in Section 9.1. Descriptive statistics will be provided for selected demographic, safety, imaging, and cytokine assessments by dose and time as appropriate. Descriptive statistics on continuous data will include means, medians, standard deviations, and ranges, while categorical data will be summarized using frequency counts and percentages. Graphical summaries of the data may be presented.

The safety profile will be based on AEs reported, vital signs measurements, clinical laboratory measurements, ECG recordings, and physical examination results. AEs associated with the first or the second infusion will be reported separately.

Adverse Events – All AEs will be listed and coded by the Medical Dictionary for Regulatory Activities (MedDRA). The number and percent of subjects reporting any AEs will be tabulated by system organ class and preferred term and categorized by dose. Adverse events will be further classified by severity, relationship to treatment, and seriousness in tabulation. Tables and/or narratives of any on-study death, or serious or significant AEs, including early withdrawals because of AEs, will be provided should they occur.

Vital Signs – Vital signs will be listed and reviewed for each subject. Depending on the size and the scope of changes, summaries of vital signs data over time and/or changes from pre-infusion value over time may be provided.

Electrocardiogram – Electrocardiogram data will be listed and reviewed for each subject. Fridericia's and Bazett's correction will be used to adjust QT for RR. Summaries of ECG intervals and/or the change from baseline will be provided. Baseline ECG parameters will be based on the mean of the Screening and pre-dose ECG assessments.

T cell Phenotype and Cytokines –The results will be listed.

Clinical Laboratory Tests – Clinical chemistry, hematology, and urinalysis data will be listed for each subject. Values outside the normal laboratory reference ranges will be flagged as high or low on the listings. Laboratory abnormalities will be graded using CTCAE v4.0. Each subject's maximum post-baseline grade will be computed for each laboratory parameter and referred to as their worst grade for that laboratory parameter. For each parameter, shift tables from baseline to worst grade may be presented.

11.5. Statistical Methods for Efficacy Endpoints

To determine the effect of the treatment of MAGE-A10^{c796}T cell infusion on tumor response and progression, summaries of efficacy will be based on ORR; best overall response; time to and duration of response; duration of stable disease; PFS; and OS. Details will be described in the SAP.

The primary efficacy endpoint is ORR defined as the proportion of subjects with a confirmed CR or PR per RECIST v1.1 relative to the total number of subjects in the corresponding analysis population. Investigator data will be used for efficacy analysis (no independent review planned unless warranted). The 95% exact confidence intervals (CI) for ORR will be calculated.

Key Secondary Analyses –The duration of response based on RECIST v1.1 will be summarized descriptively for subjects for each group using Kaplan-Meier Product Limit methods for quartile estimates. Duration of response is defined, for the subset of subjects with a confirmed CR or PR, as the time from first documented evidence of CR or PR until first documented disease progression or death due to any cause.

In addition, PFS, defined as the interval between the date of first dose and the earliest date of disease progression or death due to any cause, and OS will be summarized by cohort using Kaplan-Meier Product Limit Method for quartile estimates.

Further details about the efficacy analyses for these and other secondary endpoints, such as, how missing values will be handled and rules for censoring, will be provided in the SAP.

12. CLINICAL SUPPLIES

12.1. Packaging and Labelling

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

Labels will include batch number, protocol number, number of transduced cells, the subject's unique study identification number and any other applicable requirements.

12.2. Standard Policies and Product Return

Investigational product 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 assistants have access. Investigational product is to be dispensed only in accordance with the protocol. The Investigator is responsible for keeping accurate records of the investigational product received from the Sponsor, the amount dispensed to and any

unused investigational product remaining at the conclusion of the study. The Sponsor or designee should be contacted regarding any questions concerning the investigational product.

Sites should contact the Sponsor or designee for specific instructions for investigational product returns or destruction and appropriate documentation for drug accountability.

12.3. Storage and Handling

The subject's T cell product received at the site from the manufacturer will be stored at below —130°C until being ordered by the Investigator (or designee) to be infused. The cells will be thawed and infused as specified in Section 5.3.

12.4. Product Accountability

The investigational product provided for this study is for use only as directed in the protocol. It is the Investigator/Institution's responsibility to establish a system for handling the investigational product to ensure:

- Deliveries of the investigational product are correctly received by a responsible person
- Such deliveries are recorded
- Investigational product is handled and stored safely and properly as stated on the label
- Investigational product is only dispensed to study subjects in accordance with the protocol
- Any unused product is accounted for in the site's records before returning to the Sponsor (or designee)

At the end of the study, it must be possible to reconcile delivery records with records of usage and destroyed stock. Records of usage should include the identification of the person to whom the investigational product was dispensed, the quantity and date of dispensing. This record is in addition to any investigational product accountability information recorded on the eCRF. Any discrepancies must be accounted for on the appropriate forms.

13. DATA HANDLING AND RECORD KEEPING

13.1. Data Management

An 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. Contract Research Organization (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 using their 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 Sponsor and the sites.

13.2. Case Report Forms

For each subject enrolled, the completed eCRF must be reviewed and signed by the Investigator 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.

13.3. Site Documentation and Background 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 separate 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 informed consent forms. In no circumstances is the eCRF to be considered as source data for this trial.

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.

13.4. 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.

14. STUDY MONITORING

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

It is understood that 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 the 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 to ensure that any discrepancies detected are resolved.

14.1. 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, investigational product 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.

15. REGULATORY AND ETHICAL CONSIDERATIONS

15.1. 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.

15.2. 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 will be implemented immediately.

15.3. Local Regulations/ Declaration of Helsinki

The Investigator will ensure this study is conducted in full compliance with the principals of the "Declaration of Helsinki" or with the laws and regulations of the country in which the research is conducted, whichever, affords the greater protections 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.

15.4. 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 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 consent form 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.

15.5. 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.

15.6. 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.

15.7. Completion of the Study and Study Termination

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.

15.8. 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.

15.9. 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 International Committee of Medical Journal Editors (ICMJE) guidelines and/or publication guidelines if applicable.

15.10. Clinical Study Report

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

16. APPENDICES

APPENDIX 1. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

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

Abbreviations and Specialist Terms

ACT	Adoptive T Cell Therapy
AE	Adverse Event
ALK	Anaplastic lymphoma kinase receptor
ALT	Alanine aminotransferase
ANC	Absolute Neutrophil Count
ASCO	American Society of Clinical Oncology
CAR	Chimeric Antigen Receptor
CNS	Central Nervous System
CR	Complete Response
CRO	Contract Research Organization
CRS	Cytokine release syndrome
CT	Computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose Limiting Toxicity
DNA	Deoxyribonucleic acid
DTPA	Diethylene Triamine Pentaacetic Acid
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EDTA	Ethylenediamineteraacetic acid
EGFR	Epidermal growth factor receptor
EMA	European Medicines Agency
ES	Encephalopathy Syndrome
FDA	Food and Drug Administration
FDG-PET	18-fluorodeoxyglucose positron emission tomography
FPCP	Female patient of childbearing potential
GCP	Good clinical practice
G-CSF	Granulocyte-colony stimulating factor
GFR	Glomerular filtration rate
GVHD	Graft-Versus-Host Disease
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HTLV	Human T-cell Lymphotropic Virus
ICF	Informed consent form
ICH	International Council on Harmonization
IEC	Independent Ethics Committee
IHC	Immunohistochemistry

IND	Investigational New Drug
IRB	Institutional Review Board
ISF	Investigator Site File
ITU	Intensive Care Unit
IV	Intravenous
LTFU	Long-term follow up
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
MUGA	Multigated acquisition scan
NCI	National Cancer Institute
NIH	National Institutes of Health
NSCLC	Non-small cell lung cancer
OS	Overall survival
ORR	Overall response rate
PBMC	Peripheral blood mononuclear cell
PCR	Polymerase chain reaction
PD	Progressive disease
PFS	Progression free survival
PR	Partial response
Psi	Packaging signal
RCL	Replication competent lentivirus
RCR	Replication competent retrovirus
RNA	Ribonucleic acid
SAE	Serious adverse event
SD	Stable Disease
SIN	Self-inactivating
SPM	Study Procedures Manual
SRC	Safety Review Committee
SRS	Stereotactic Radiosurgery
TCR	T cell receptor
TIL	Tumor-infiltrating lymphocyte
TKI	Tyrosine kinase inhibitor
ULN	Upper limits of normal
USPI	United States product insert
WBRT	Whole Brain Radiotherapy

APPENDIX 2. 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

Source: (Oken, 1982).

APPENDIX 3. LOCAL LABORATORY TESTS AND ECG PARAMETERS

Clinical Chemistry:	Calcium Phosphorus Magnesium Albumin Bilirubin Alanine aminotransferase Aspartate aminotransferase Alkaline phosphatase Lactic acid dehydrogenase Sodium Potassium Bicarbonate/CO_2 Creatinine* Chloride Glucose Urea/BUN Amylase (baseline only) Lipase (baseline only) *Creatinine clearance will be calculated using the Cockcroft-Gault Method or by 24-hour urine creatinine collection or by nuclear medicine EDTA GFR measurement, or DTPA according to standard practice at the treating institution.
Hematology:	Red cell count Hemoglobin Hematocrit Mean cell volume Mean corpuscular hemoglobin Mean corpuscular hemoglobin concentration Platelet count White blood cell count & differential count (percent & absolute)
Lymphocyte subset	Absolute cell count and percentage of CD3, CD4, and CD8
Coagulation Screen:	Prothrombin time *or* International Normalized Ratio Activated partial tissue thromboplastin time

Infectious disease markers:	HIV 1+2 antibody* 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 / DNA PCR* EBV (EBNA)* Syphilis (spirochaete bacterium) rapid plasma regain* *Changes to specific tests listed are acceptable per institutional standard practice **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
Pregnancy Test:	Serum β-hCG or Urine test
Thyroid Function Tests:	TSH with reflex free T4
Other Tests:	Uric acid C-reactive protein Cardiac troponin (cTnI or cTnT)
ECG Parameters:	Heart Rate Heart Rhythm PR Interval RR Interval QRS Interval QTc Interval (Fridericia's or Bazett's correction)
Urinalysis:	Glucose Ketones Specific gravity Protein Blood Microscopy Bilirubin pH

APPENDIX 4. 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 efficacy assessments.

Lesions on a chest X-ray may be considered measurable lesions if they are clearly defined and surrounded by aerated lung. However, CT is preferable. 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).
- 20 mm by chest X-ray.

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, and 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 progression.

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.

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 (Stable Disease, SD): 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. In patients with symptomatic deterioration of disease, every effort should be made to document objective progression by evaluation of target and non-target lesions. Patients with a global deterioration of health status without objective evidence of disease progression at that time should be reported as clinical progression.

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 complete response 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'.

Special notes on the assessment of 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 initial scan.
- 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 18-fluorodeoxyglucose positron emission tomography (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*
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR Non-PD Not evaluated	No	PR	
SD	Non-CR Non-PD Not evaluated	No	SD	Documented at least once ≥4 wks. ± 3 days from Baseline**
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 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.

APPENDIX 5. SCHEDULE OF PROCEDURES FOR SECOND T CELL INFUSION (INTERVENTIONAL PHASE INFUSION 2)

Table 17: Schedule of Procedures for Second T Cell Infusion (Interventional Phase Infusion 2)

		Interventional Phase Infusion 2																						Completion/ Withdrawal[5]
	Baseline[1]	Lymphodepleting Chemotherapy[2]				T-cell in-fusion[3]	Post-T-cell Infusion																	
Day (D) / Week (W)	-28 D[4] of Chemo-therapy	D -7	D -6	D -5	D -4	D1	D 2	D3	D 4	D 5	D 8	D 10 & 12	W2	W3	W4	W5	W6	W8	W10	W12	W16	W24	Every 3 Mos Until Yr 2.	Every 6 Mos There-after	
Visit Window		n/a	n/a	n/a		n/a	±1 day						±3 days					±7 days					±14 days	±3 mos	n/a
Visit	1	2	3	4	5	6	7	8	9	10	11	12/13	14	15	16	17	18	19	20	21	22	23	24-29	30+	
Clinical Assessments and Procedures[6] (refer to Section 7.4 for details)																									
Informed Consent[7]	X																								
Inclusion/ Exclusion	X[8]																								
Medical History[9]	X																								
Physical Exam	X					X					X		X									X	X	X	
Prior/Concomitant	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	v	X	X	X
ECOG	X					X					X		X	X	X		X	X		X	X	X	X	X	X
Vital Signs / Height/	X					X[12]	X	X	X	X	X		X												X
ECG	X					X	X		X		X														
CT / MRI [13]	X														X			X		X		X	X	X	X

	Baseline[1]	Interventional Phase Infusion 2																						Completion/ Withdrawal[5]
		Lymphodepleting Chemotherapy[2]				T-cell in-fusion[3]	Post-T-cell Infusion																	
Day (D) / Week (W)	**-28 D[4] of Chemo-therapy**	**D -7**	**D -6**	**D -5**	**D -4**	**D1**	**D 2**	**D3**	**D 4**	**D 5**	**D 8**	**D 10 & 12**	**W2**	**W3**	**W4**	**W5**	**W6**	**W8**	**W10**	**W12**	**W16**	**W24**	**Every 3 Mos Until Yr 2.**	**Every 6 Mos There-after**	
Visit Window		**n/a**	**n/a**	**n/a**		**n/a**	**±1 day**						**±3 days**					**±7 days**					**±14 days**	**±3 mos**	**n/a**
Visit	1	2	3	4	5	6	7	8	9	10	11	12/13	14	15	16	17	18	19	20	21	22	23	24-29	30+	
Brain MRI[13]	X																								
Chest X-ray	X																								
PFTs[14]	X																								
Telemetry monitoring						X[27]																			
CARTOX-10						X[28]	X	X	X	X	X														
Lymphocyte subset (CD3/CD4/CD8)[26]	X																								
Hematology	X[4]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chemistry	X[4]	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X		X	X	X	X	X	X
Amylase, Lipase	X																								

	Baseline[1]	Interventional Phase Infusion 2																						Completion/ Withdrawal[5]
		Lymphodepleting Chemotherapy[2]				T-cell in-fusion[3]	Post-T-cell Infusion																	
Day (D) / Week (W)	**-28 D[4] of Chemo-therapy**	**D -7**	**D -6**	**D -5**	**D -4**	**D1**	**D 2**	**D3**	**D 4**	**D 5**	**D 8**	**D 10 & 12**	**W2**	**W3**	**W4**	**W5**	**W6**	**W8**	**W10**	**W12**	**W16**	**W24**	**Every 3 Mos Until Yr 2.**	**Every 6 Mos Thereafter**	
Visit Window		**n/a**	**n/a**	**n/a**		**n/a**	**±1 day**						**±3 days**					**±7 days**					**±14 days**	**±3 mos**	**n/a**
Visit	1	2	3	4	5	6	7	8	9	10	11	12/13	14	15	16	17	18	19	20	21	22	23	24-29	30+	
Coagulation Tests	X[4]																								
Pregnancy Test[15]	X																								
Urinalysis	X[4]																								
Infectious disease markers[16]	X																								
CMV IgG and PCR[17]	X					X							X		X		X	X							
TSH with free T4[18]	X																								
CRP[19]	X					X			X		X		X		X										
Uric acid	X					X												`							
GFR or 24h urine[20]	X																								
Adverse Events[21]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

	Baseline[1]	Interventional Phase Infusion 2																						Completion/ Withdrawal[5]
		Lymphodepleting Chemotherapy[2]				T-cell in-fusion[3]	Post-T-cell Infusion																	
Day (D) / Week (W)	**-28 D[4] of Chemo-therapy**	**D -7**	**D -6**	**D -5**	**D -4**	**D1**	**D 2**	**D3**	**D 4**	**D 5**	**D 8**	**D 10 & 12**	**W2**	**W3**	**W4**	**W5**	**W6**	**W8**	**W10**	**W12**	**W16**	**W24**	**Every 3 Mos Until Yr 2.**	**Every 6 Mos There-after**	
Visit Window		**n/a**	**n/a**	**n/a**		**n/a**	**±1 day**						**±3 days**					**±7 days**					**±14 days**	**±3 mos**	**n/a**
Visit	1	2	3	4	5	6	7	8	9	10	11	12/13	14	15	16	17	18	19	20	21	22	23	24-29	30+	
Overall survival	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vector Copies (Persistence for Safety)[22]	X																					X		X[22]	
VSV-G DNA (RCL)[23]	X																			X		X		X[23]	
Lymphodepleting Chemotherapy[2] & Investigational Product Administration																									
Fludarabine		X	X	X	X																				
Cyclophos-phamide				X	X																				
MAGE-A10^{c796}T[25]						X																			
Correlative Studies and Research Assessments (refer to Section 7.5 for details)																									
Tumor biopsy[24]	X[24a]													X											X

		Interventional Phase Infusion 2																						Completion/ Withdrawal[5]
	Baseline[1]	Lymphodepleting Chemotherapy[2]				T-cell in-fusion[3]	Post-T-cell Infusion																	
Day (D) / Week (W)	-28 D[4] of Chemo-therapy	D -7	D -6	D -5	D -4	D1	D 2	D3	D 4	D 5	D 8	D 10 & 12	W2	W3	W4	W5	W6	W8	W10	W12	W16	W24	Every 3 Mos Until Yr 2.	Every 6 Mos There-after	
Visit Window		n/a	n/a	n/a		n/a	±1 day						±3 days					±7 days					±14 days	±3 mos	n/a
Visit	1	2	3	4	5	6	7	8	9	10	11	12/13	14	15	16	17	18	19	20	21	22	23	24-29	30+	
[redacted]																									
[redacted]																									
[redacted]																									
[redacted]																									

Abbreviations: CMV = cytomegalovirus; CRP = C-reactive protein; CRS = cytokine release syndrome; CT = computed tomography; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; FPCP = female patient of childbearing potential; MRI = magnetic resonance imaging; n/a=not applicable; PCR = polymerase chain reaction; PFT = pulmonary function test; RCL = replication competent lentivirus; TSH = thyroid-stimulating hormone; VSV-G =vesicular stomatitis virus G protein

1 Subjects must have been considered eligible for a second infusion (refer to Section 4.4) before initiating any Screening procedures or assessments for Interventional Phase Infusion 2.
2 Refer to Section 5.2 for details on prophylaxis therapies, pre-medications, fludarabine dose adjustments according to renal function, and supportive treatments.
3 All samples will be collected and assessments performed prior to T-cell infusion, unless otherwise specified.
4 Clinical procedures or assessments do not need to be repeated at this Baseline visit if they were be performed within 28 days of planned leukapheresis, with the exception of lymphocyte subset (CD3/CD4/CD8), hematology, chemistry, coagulation and urinalysis which must be done within 7 days of leukapheresis. ECG and ECHO/MUGA do not need to be repeated prior to lymphodepletion unless patient is symptomatic or has had therapy known to adversely affect cardiac function.
5 If a subject withdraws consent or ends the Interventional Phase Infusion 2, all procedures and assessments listed at this visit must be performed, unless done within the previous 30 days.
6 All clinical assessments and procedures must be performed as indicated; however, any clinical assessment or procedure can be performed if clinically indicated at any time.
7 An additional written subject informed consent for a second infusion must be obtained prior to performing any Baseline assessments or procedures, unless otherwise specified.
8 Subjects must continue to meet all eligibility criteria (Section 4.2 and Section 4.3) in addition to meeting those prior to second infusion specified in Section 4.4).
9 Any new or changes in medical history will be recorded in the EDC at Baseline visit; however, any additional changes in medical history must be recorded in source documents throughout the conduct of the study.
10 Includes all prescription, over-the-counter medications, and herbal remedies. Any use of mutagenic agents or investigational agents must also be reported.
11 Includes temperature, blood pressure, pulse rate, respiratory rate, and oxygen saturation. Height will be collected at the Screening visit only.
12 Vital signs on day of T cell infusion should be taken pre-infusion, and at 15 and 30 minutes, and 1, 1.5, 2, and 4 hours after the infusion has started.
13 If a subject is found to have a tumor response or PD by imaging, a follow-up confirmation scan must be done no earlier than 4 weeks following the scan when response or PD first seen. A subject is not considered to have a response or PD until follow-up scan confirms the finding. If there is unequivocal evidence of PD and/ or the need for an alternate anti-cancer treatment a confirmatory scan is not required. Brain MRI will be performed at baseline. If CNS metastases are detected at baseline a brain MRI should be performed at all subsequent CT/MRI visits, and if clinically indicated. See Section 7.4.7.
14 Includes FEV1, FVC, TLC, and DLCO parameters to determine eligibility as described in Exclusion criterion #9.
15 FPCP must have a negative urine or serum pregnancy test.
16 Includes HIV, HBV, HCV, HTLV, EBV, and syphilis (spirochaete bacterium). Refer to Exclusion criterion #11 for details on required testing for eligibility.
17 Only subjects who are CMV IgG seropositive at Baseline will continue to be monitored for CMV viremia by CMV DNA PCR post Baseline.
18 A free T4 test should be performed in subjects who have an abnormal TSH function test (high or low).
19 If CRS is suspected, cytokine and C-reactive protein levels should be measured approximately every other day until symptoms are improving or an alternative diagnosis is confirmed.
20 Creatinine clearance will be calculated using the Cockcroft-Gault Method or by 24-hour urine creatinine collection or by EDTA GFR measurement, or DTPA according to standard practice at the treating Institution.
21 Adverse events should be reported as noted in Section 9.1.
22 Persistence for safety of gene modified cells in subjects will be monitored at Baseline,Months 6, and 12 post-infusion, then every 6 months until 5 years post-infusion and annually from year 6-15 post infusion. If no gene modified cells are detected for 3 consecutive assessments post-infusion, and subject is >5 years post-infusion, then sample collection may stop.

[redacted] However, if VSV-G DNA copies are detected at any time point in the first year post-infusion, refer to the safety monitoring procedures in Section 10.1.2.

24 Core needle biopsies are at Baseline, week 3 (+5 weeks), and at or after confirmation of PD, with the exception of subjects for whom there is no safely accessible tumor tissue. 24a.) If a fresh biopsy was taken to confirm continued expression of MAGE-A10 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. 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. 24b.) To allow for parallel collection, the baseline biopsy sample may also be taken from two months up to one week before lymphodepletion, and the week 4 OR week 8 liquid biopsy collection may be performed at the same time as the week 3 (+5 weeks) core needle biopsy. .

25 Subjects will receive the MAGE-A10^{c796}T cell dose level deemed to be safe and as defined in Table 1.

26 Lymphocyte subset is recommended but not required if sites cannot test this in their local laboratory.

27 For subjects with known cardiac or pericardial tumor involvement at baseline, inpatient telemetry monitoring should be carried out for a minimum of seven days post MAGE-A10 infusion

28 CARTOX-10 assessment must be done prior to T-cell infusion on Day 1. Refer to Section 8.8 for further details including when additional assessments may be required.

APPENDIX 6. LIST OF REFERENCES

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APPENDIX 7. PROTOCOL CHANGES

Amendment 13 Changes

Global Protocol Amendment 11 dated, 27 February 2019, is replaced by Global Amendment No. 13, Protocol, dated 14 June 2019. This amendment applies to all participating investigative sites apart from the UK sites.

Table 18: Summary and Rationale of Protocol Changes

Sections changed	Protocol Change	Rationale
1.4.1	Clarified the lymphodeleting chemotherapy data seen in the NY-ESO-1 study was evaluated in sarcoma subjects.	For clarification.
1.4.1, 3.1, 3.2.3, 5.2, 7.2, 8.9.1	Change to the lymphodepleting chemotherapy regimen for the Expansion Group – cyclophosphamide dose changed from 1800mg/m^2/day on days -3, -2, to 600mg/m^2 on days -7, -6, and -5 and G-CSF administration changed to Day -3	Review of recent emerging safety data, all future patients treated in the Expansion Group will be treated with the Dose Group 3 lymphodepletion regimen. Justification provided in Section 1.4.1
3.1, 5.2, 8.9.1	G-CSF administration is required and was previously 'recommended' after lymphodepleting chemotherapy.	Administration of G-CSF was changed per ASCO Guidelines (Smith 2015) for prevention of febrile neutropenia in patients at high risk on the basis of myelotoxicity of the chemotherapy regimen.
Synopsis, 4.2	Inclusion Criteria #3 add an upper limit to age to ≤75 years. Inclusion Criteria #14, increased ANC, platelet and renal. Exclusion Criteria #9 added exclusion language regarding significant history of cardiovascular disorders.	Eligibility criteria in the protocol were changed based on recent safety data and events.
5.2.1	Fludarabine dose adjustment for renal impairment updated	Updated per Inclusion Criteria #14
5.4, 7.5.2, Appendix 5	Clarified biopsy collection windows for Baseline and Week 3 time points	Updated for clarification
3.3, 4.7	'Stopping Rules' removed from the title in Section 3.3 because it is discussed in Section 4.7 Stopping rules was updated for any death 'possibly' related to the	Protocol correction An event with a possible relationship is not sufficient to

	MAGE-A10^{c796}T to 'probably' related	result in suspension of enrollment. This action should be reserved for events with a higher likelihood of relationship to the MAGE-A10c796T cell product, especially given the comorbidities and concurrent therapies in the treatment population